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Immune Cell Trafficking to the Liver

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Abstract

The human liver is an organ with a diverse array of immunologic functions. Its unique anatomic position that leads to it receiving all the mesenteric venous blood, combined with its unique micro anatomy, allows it to serve as a sentinel for the body's immune system. Hepatocytes, biliary epithelial cells, Kupffer cells, stellate cells, and liver sinusoidal endothelial cells express key molecules that recruit and activate innate and adaptive immunity. Additionally, a diverse array of lymphoid and myeloid immune cells resides within and traffic to the liver in specific circumstances. Derangement of these trafficking mechanisms underlie the pathophysiology of autoimmune liver diseases, NASH, and liver transplantation. Here, we review these pathways and interactions along with potential targets that have been identified to be exploited for therapeutic purposes.

Keywords

Liver immunology; chemotaxis; immunobiology

INTRODUCTION

The liver is responsible for numerous important tasks that support and impact all organ systems. It is essential for the metabolism of carbohydrates, lipids, amino acids, and vitamins as well as the storage of nutrients. The liver also plays a key role in digestion, producing bile that allows for absorption of lipids. Additionally, it is responsible for the breakdown and clearance of numerous toxic substances and drugs. Early in fetal development, the liver is also responsible for hematopoiesis. Although not often thought of as such, the liver is a unique and complex immunologic organ as well. The liver houses a diverse population of immune cells despite not being considered a lymphoid organ and is responsible for the production of acute phase proteins important for immune responses.[1,2] Here, we will review the unique aspects of the liver and its array of resident immune cells and functions, as well as the specialized mechanisms that have developed in order to direct immune cells to the liver in both normal and pathologic conditions.

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ANATOMY OF LIVER AS AN IMMUNOLOGIC ORGAN

Gross Blood Supply

The liver receives 80% of its blood supply from mesenteric venous circulation and 20% from the systemic arterial circulation (Figure 1). This not only supplies the liver with nutrients from the gastrointestinal (GI) tract, but also signaling molecules, intact cells and microorganisms from both intestinal and systemic circulation that facilitate its metabolic, detoxification, and immunologic functions. Potentially pathogenic and malignant cells are carried to the liver via mesenteric circulation, while systemic antigens are brought to the liver via arterial circulation. With this constant inundation of pro-inflammatory antigens, the liver has developed mechanisms to remain in a homeostatic state and to allow for pro-inflammatory response only when appropriate.[3,4] For example, animal models have shown that antigens are better tolerated when introduced via the portal vein versus systemic circulation, proving the liver's protective role from over-inflammation.[5]

Microcirculation

Both the arterial and portal circulation terminate into the same thin, porous network of specialized capillaries made up of liver sinusoidal endothelial cells (LSECs).[6] The liver sinusoids lack a basement membrane and instead have a subendothelial compartment, called the space of Disse, where lymph collects into lymphatics.[7] Blood drains through the fenestrations within the sinusoids, passing through the space of Disse and to hepatic parenchymal cells (Figure 2). Blood flow is very slow within the sinusoids allowing for longer exposure of antigens within the sinusoids.[8] This network of slow-flowing capillaries facilitates the recognition and processing of antigens by the many immune as well as non-immune cells within the liver.

IMMUNE FUNCTION OF LIVER CELLS

Hepatocytes comprise approximately 80% of the cells within the liver (Figure 3). They are the main drivers of the liver's metabolic functions and are responsible for protein synthesis, carbohydrate storage and transformation, synthesis of bile and lipids, detoxification and processing of drugs. Although they are not immune cells, hepatocytes express innate immune receptors and can serve as antigen-presenting cells (APCs).[9] They constantly express intercellular adhesion molecules and can be induced to express moderate levels of human leukocyte antigen (HLA) class I molecules.[10] With high doses of interferon gamma (IFNγ), such as in an inflammatory state, hepatocytes express HLA class II molecules *in vitro*.[11] They can prime naïve CD3+CD8+ T cells and numerous *in vivo* experiments have confirmed hepatocytes' ability to serve as APCs.[11–13]

LSECs also play a unique role in physiological tolerance and hepatic immune reactivity. At rest, human LSECs express intercellular adhesion molecule-1 (ICAM-1) at a detectable level; however stimulation by tumor necrosis factor alpha (TNFα) and IFNγ induces increased expression of ICAM-1 as well high levels of major histocompatibility complex (MHC) Class II, CD40, and vascular cell adhesion molecule-1 (VCAM-1) that are previously unexpressed at rest, priming LSECs to interact with immune cells.[14]

Additionally, they have the ability to express other molecules necessary for antigen presentation including CD11b, CD11c, CD40, CD80, and CD86 in mice.[15–24] Antigen presentation by LSECs normally leads to an anti-inflammatory, homeostatic environment. In mice, primed LSECs induce tolerant antigen-specific CD8+ T cells that is conserved following adoptive transfer from ovalbumin-fed to unfed mice.[25,26] Endotoxin in liver downregulates expression of MHC class II, CD80 and CD86, but induces IL-10 secretion which suppresses murine LSECs' antigen-presenting ability. LSECs also fail to induce activation of naïve CD4+ T cells in the presence of lipopolysaccharide (LPS).[27–29] Data also suggest that Fas/Fas ligand and programmed death (PD)-1 ligation pathways are important and that LSECs can suppress dendritic cell (DC) activation of naïve CD8+ T cells through direct contact, but the underlying mechanism remains unclear.[16,30,31] These interactions leads a relative resistance of the normal inflammatory activation by LPS seen in other tissues and a net regulatory effect by LSECs. However, in the setting of chronic liver diseases, LSECs become pro-inflammatory and no longer promote homeostatic conditions. In mice, after fibrotic injury caused by hepatotoxins, antigen presentation by LSECs induces IFNγ, IL-6, and TNFα secretion and an immunogenic T cell phenotype.[28] Additionally in a murine model of hepatitis, infection of mouse hepatitis virus 3 and attenuated variants led to LSECs to release more pro-inflammatory factors and less IL-10 through TLR2 dependent pathways.[32] Although the precise role LSECs play in infection remains unclear, they certainly are important mediators of continuing liver injury in settings of chronic liver disease.

The liver is also an important reservoir of macrophages, with 80–90% of the body's total macrophages consisting of Kupffer cells (KCs) that reside within the hepatic sinusoids.[33] Unlike other macrophages, KCs express a unique complement receptor that binds C3b, allowing them to catch bacteria under flow and shear conditions.[34–36] However, these pathogens are only captured and held in place to be killed by neutrophils and other immune cells.[37] Although they express the necessary markers to activate T cells, continuous exposure to LPS reduces KCs ability to activate lymphocytes.[15,28,38] They can become potent activators of T cells in the presence of other pathogen-associated molecules or inflammatory cytokines.[39] Additionally, they capture and clear activated neutrophils and depending on which receptor complex activates them, KCs can produce either pro- or anti-inflammatory cytokines in order to regulate inflammation and protect from collateral damage.[40,41]

DCs are also localized throughout the parenchyma but are mostly concentrated around the central vein where they lie in wait rather than patrol within tissues.[42] Unlike their counterparts in other tissues, and consistent with the high-LPS environment in which they reside, hepatic DCs require much higher levels of LPS in order to activate T cells. Under basal conditions, they have an immature phenotype lacking costimulatory molecules necessary for T cell activation.[43] The cytokine milieu within the liver, where IL-10 is high and IL-12 low, contributes to relative tolerance by promoting a shift from helper T cell (Th)1 to Th2 responses and the development of regulatory T cells (Tregs). However, DCs also have a greater capacity for phagocytosis and production of cytokines.[44,45] The potential for robust activation of T cells resides within all hepatic DCs and is realized with blockage of IL-10 or activation by pathogen-associated molecules that leads to increased expression of co-stimulatory molecules.[46] In fact, such stress is required for DCs to stimulate liver regeneration, as this is impaired in mice that are germ-free and resistant to LPS.[47]

Stellate cells (HSCs), also known as Ito cells, also play an immunologic role. Residing within space of Disse, under normal conditions they have a central role in vitamin A and lipid storage. Like other resident cells in the liver, HSCs express the prerequisite molecules for antigen presentation, but at insignificant levels under basal conditions.[48–50] Although they have the ability to endocytose exogenous antigens, the mechanism for this remains unknown. Under inflammatory conditions, stellate cells differentiate into myofibroblasts that lead to liver fibrosis in chronic liver disease. There is some evidence that their ability to present antigens and directly activate T, natural killer (NK), and natural killer T (NKT) cells also is enhanced in such disease states.[51]

Cholangiocytes – the epithelial cells of the bile ducts – are primarily involved with secretion of bile from the liver. These cells are targeted in cholangiopathies, such as primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). These cells also have secondary roles in liver immunity. Being contiguous with the intestinal epithelium, they share similar mucosal immune functions, such as secretion of IgA.[52] *In vitro* and *in vivo* studies have revealed that human cholangiocytes express ICAM-1, VCAM-1, lymphocyte function associated antigen (LFA)-3, HLA-I and HLA-II.[53–56] They also possess the necessary co-stimulation molecules necessary for antigen presentation, albeit at very low levels.[57] Additionally, cholangiocytes participate in recruitment of immune cells via cytokine and endotoxin induced expression of CXCL8, CX3CL1, CXCL12, and CXCL16.[58–61]

The liver is rich in lymphocytes with about 10^{10} cells in an average liver. They reside within the portal tracts, sinusoids, as well as throughout the parenchyma.[62–65] The vast majority of lymphocytes are CD3+CD56− T cells, CD3−CD56+ NK cells, and CD3+CD56+ NKT cells. Only approximately 5% of lymphocytes are B cells. Although the same populations are present in the peripheral circulation, the liver-resident lymphocytes vastly differ in the proportions of the different sub-types. Conventional αβ T cells comprise about 80% of CD3+ lymphocytes, with γδ cells comprising the remainder. This is in contrast to the periphery, where the proportion of γδ cells is 5-times lower.[66,67] The role of γδ cells in liver immune homeostasis remains unclear, however there is evidence that it is mediated via IL-17A pathways.[68] The population of conventional T cells is also enriched in CD8 cells, with a reversal of the normal 2:1 CD4:CD8 ratio seen in the periphery. Most CD8 T cells have an activated phenotype, expressing CD25 and CD69.[69] NK and NKT cells in the liver make up a much larger proportion of lymphocytes when compared to the periphery. NK cells comprise one-third to one-half of hepatic lymphoid cells, three times greater than in periphery.[70] They release cytotoxic granules as well as large amounts of cytokines, especially IFNγ, to direct immune responses.[71] NKT cells produce cytokines to promote either inflammatory or anti-inflammatory responses and they are also the only immune cells that actively patrol the sinusoids, seeking out antigen.[72,73]

TRAFFICKING OF IMMUNE CELLS TO THE LIVER

Pattern Recognition Receptors

Trafficking to the liver begins with the recognition of antigens by one of the many types of immune cells described above. Hepatocytes, LSECs, HSCs, KCs, and lymphocytes express

pattern recognition receptors (PRR) that recognize and bind microbial-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that are abundant on the immunogenic molecules the liver is exposed to.[74–76] It is the recognition of PAMPs and DAMPs that is the basis for targeted responses of the immune system. A specialized group of PRRs called the Toll-like receptors (TLRs) are the best characterized group. This family of PRRs recognize many different pathogenic molecules including LPS, bacterial flagella, and both RNA and DNA derived from bacteria and viruses. Depending on the type of TLR involved, binding can lead to activation, cytokine production and release, and modulation of many other cellular functions.[9,77] Unlike elsewhere in the body, binding of TLRs in the liver usually promotes immunosuppressive effects to prevent over-inflammation in response to bacterial and dietary antigens the liver is exposed to regularly, especially for LPS via the TLR4 pathway. However, TLR-mediated immune regulation can be overcome by stimulation via other TLR-subtypes by non-LPS molecules such as flagella (via TLR5), viral double-stranded RNA (via TLR3), and single-stranded RNA (via TLR7 and TLR8).[39,78–80]

LSECs have abundant expression of both scavenger and carbohydrate receptors. Scavenger receptors recognize targets via glycosylation patterns, peptide motifs, and lipid moieties. These ligands can be internalized via endocytosis and processed to be presented to immune cells.[81,82] These receptors are involved in the recognition of *Mycobacterium tuberculosis* and serve as an entry point for hepatitis C virus (HCV).[83–85] LSECs also highly express carbohydrate receptors that recognize specific sugar moieties such as N-acetylglucosamine and mannose which are present on both self and non-self molecules.[86] These receptors mediate internalization of *Candida, M. tuberculosis*, and other pathogens.[87,88]

Hepatic immune cells are capable of humoral immune system interactions through the expression of receptors for immunoglobulin (FcRs) and for complement. Both KCs and LSECs express FcRs that, upon binding of its ligand, facilitate phagocytosis of the target and modulation of cellular function depending on the type of FcR bound. KCs preferentially bind larger immune complexes while LSECs bind smaller complexes via FcRs.[89–92] Many different complement receptors are expressed by KCs, including a special class of receptor localized only to the liver (and possibly splenic macrophages) called complement receptor of the immunoglobulin superfamily (CRIg).[35] This receptor mediates the capture and clearance of C3b coated bacterial and viral targets allowing KCs to bind them under shear conditions and contributing to the sentinel role they play in the immune system.[36,93]

Adhesion Molecules

For leukocytes to act on invasive pathogens, migration must first occur from blood vessels into target tissues. Initial interactions occur between leukocytes and endothelial cells via a rolling interaction. In most organs, this takes place in post-capillary venules and is mediated by selectins, a family of adhesion proteins found on leukocytes (L-selectin), endothelial (E-selectin) cells, as well as platelets (P-selectin).[94] These adhesion molecules are constitutively expressed and bind glycans on leukocytes to mediate tethering and rolling in organs.[95] These are relatively weak interactions that are followed by tighter interactions mediated by integrins on immune cells and their ligands on endothelial cells.[96] Unlike selectins, integrin expression requires activation and their affinity for their ligands can be

modified by chemokine stimuli.[96] Once leukocyte integrins bind to their respective endothelial cells, they then transmigrate from blood vessels and into tissue in most organs.

However, this model of leukocyte extravasation does not apply in the liver. Adhesion occurs within the sinusoids and actually at a much higher proportion than in post-capillary venules. These interactions occur without any notable selectin-mediated rolling.[95,97] Additionally, leukocytes do not require transmigration to interact with liver immune cells. Extensions of hepatocytes and KCs protrude through sinusoid fenestrations and directly interact with leukocytes within the lumen.[98] Therefore, the interactions between integrins on immune cells and their ligands on different liver cells are the most important mediators of immune interactions and are mediated chiefly by two families of integrins: α4 and β2.

The α4 integrin group includes α4β1 and α4β7, molecules that are expressed on lymphocytes and monocytes (Figure 4)[99]. Their ligands on endothelial cells are VCAM-1 and mucosal addressin cell adhesion molecule 1 (MadCAM-1), respectively.[99] VCAM-1 is inducible in all tissues; however the level of expression in liver under homeostatic conditions is comparable to that seen in other tissues during inflammatory conditions.[100] MadCAM-1 expression is normally expressed on intestinal endothelium, but can also be expressed by LSECs mediating liver inflammation in PSC.[101] β2 integrins are a family of adhesion molecules expressed on all types of leukocytes and mediates their firm adhesion in many tissues.[95,102,103] The most important ligand for β2 integrins is ICAM-1. In tissues outside the liver, ICAM-1 is only highly expressed in post-capillary venules; basally LSECS express ICAM-1 at similar levels to hepatic post-capillary venule, i.e. central vein.[104] Interactions between VCAM-1 on LSECS and α4β1 integrin on activated CD8 T cells mediate non-specific adhesion which in turn adhere via interactions between β2 and ICAM-1 if recognition of antigens presented by hepatocytes or LSECs occurs.[100]

Other adhesion molecules also play a role in liver immune cell trafficking. Vascular adhesion protein-1 (VAP-1) is a glycoprotein expressed by LSECs that is particularly important in the liver. It promotes shear-dependent adhesion and transmigration across hepatic sinusoids and mediates activation of LSECs to upregulate other molecules that promote immune cell recruitment.[105–109] Under homeostatic conditions, little VAP-1 is expressed but expression increases significantly in the setting of inflammation.[110] However, the adhesion molecule on leukocytes that serves as its ligand remains to be identified. CD44 is another glycoprotein expressed by leukocytes that plays an important role in trafficking immune cells to the liver. It interacts with hyaluronan that is expressed on many different cell types, including LSECs. More recently, common lymphatic endothelial and vascular endothelial receptor (CLEVER-1) has been described and found to support adhesion and migration of human lymphocytes on lymphatic vessels and endothelial venules.[111] Inhibition of CLEVER-1 reduces Treg migration into hepatic sinusoids by 40% and by >80% when ICAM-1 and VAP-1 were also inhibited.[112]

Chemokine Signals and Receptors

Chemokines are polypeptides that are secreted in response to both pro- and anti-inflammatory stimuli and bind cell-surface receptors that direct chemotaxis. They include four conserved cysteine residues that form two disulfide bonds pairing the first with the

third, and the second with the fourth cysteine residues. They are grouped into four categories based on the arrangement of the N-terminal 2 cysteine residue. They are CXC, where one amino acid separates the 1st two cysteines; CC, where the two are adjacent to each other; CX3C, where 3 amino acids are between the two residues; and (X)C where the first and third cysteines are missing.[113] Lymphocytes in the periphery express many of these receptors in homeostatic conditions.[114–120] In normal and pathologic conditions of the liver, there are many chemokine-chemokine receptor interactions that mediate pro- and anti-inflammatory responses. The chemokine receptors CXCR3, CXCR6, CCR5, CCR2 and CCR1 on liver infiltrating effector T cells are the main mediators of recruitment (Table 1).[121–124]

CXCR3 and its ligands CXCL9, CXCL10, and CXCL11 are closely linked to pro-inflammatory Th1 responses. Effector CD4+ and CD8+ T cells within liver express high levels of CXCR3.[125–127] Under inflammatory conditions, KCs and infiltrating innate immune cells release TNFα and IFNγ, which promote expression of ligands for CXCR3 by hepatocytes, HSCs, LSECs, and damaged or inflamed bile ducts.[128] CD154+ immune cells that infiltrate the liver in states of inflammation trigger secretion of CXCR3 ligands by interaction with CD40 on liver cells.[129,130] Blockade of CXCL9 and CXCL10 in mice reduces recruitment of host-derived mononuclear cells, especially those expressing CXCR3.[131] Although these molecules are important mediators for adhesion and transmigration of lymphocytes across LSECs, blockade of individual molecules only partially reduced migration of lymphocytes, indicating the presence of redundant mechanisms.[132,133] Tregs also use CXCR3-mediated processes to migrate into human liver tissue, indicating that its overall immune impact involves fine-tuning the balance of effector and regulatory cells.[134]

CXCR6 is expressed on Th1 and effector T cells in peripheral blood in homeostatic conditions, but much higher expression is found on CD4 and CD8 T cells that have infiltrated the liver. It interacts with CXCL16, regulating recruitment of activated T cells to inflamed liver in humans and mice.[61] Inflamed bile ducts, hepatocytes, and LSECs in mice highly express CXCL16 allowing them to interact with CXCR6+ inflammatory cells as well as promoting β1 integrin dependent adhesion.[135] In particular, CXCR6 is required for NK and NKT cell homing to the liver.[73] In HCV, there is a specific subset of CXCR6+CD8+ T cells that express CD161, a C-type lectin involved in NK cell function and production of IFNγ and IL-17.[136] In a mouse model of Graft vs Host Disease (GVHD), knock out of CXCR6 significantly reduces the accumulation of activated donor-derived CD8 T cells in recipient liver without changing the frequencies of CD8 T cells in peripheral circulation.[137]

CCR5, CCR2 and CCR1 have all been shown to interact with common ligands and promote recruitment of leukocytes to the liver. CCR5 interacts with CCL3, CCL4, CCL5, and CCL8; CCR2 interacts with CCL2, CC7, CCL8, and CCL13; while CCR1 interacts with CCL3, CCL5, CCL7, CCL14–16, and CCL23. Positivity for all three receptors is characteristic of memory T cells.[138,139] CD8 T cells in inflamed human livers are enriched with CCR2 and CCR5, while CCR1 has been shown to regulate hepatic inflammation in mouse models.[121,123] In portal endothelium, CCR5 is highly expressed and in mouse models of GvHD, leads to recruitment of effector cells to the portal tracts.[140–142] However, in CCR5 knockout

mice, liver inflammation is much more extensive and mediated by CCR1+ effectors, indicating that CCR5 may also recruit anti-inflammatory cells.[143] However, in humans, blockade of CCR5 reduces liver inflammation and injury in GvHD.[144]

CCR6 is also an important signal responder in leukocyte recruitment to the liver. Although deficiency in this receptor leads to an increase in the recruitment of CD4+ T cells, it leads to a reduction of IL-17+ cells in liver injury in mice.[145] Interactions with its ligand CCL20 on small intestine and inflamed bile ducts redirects Th17 cells from the periphery to these injured areas.[146] In addition to mediating recruitment of inflammatory cells, CCR6 is also responsible for inducing migration of γδ T cells in chronic injury that inhibit HSC-mediated fibrosis and dampen excessive inflammation.[147]

The CX3CR1-CXC3L1 chemokine axis is another important signaling pathway that is essential for recruitment of immune cells to the liver. CX3CL1, also known as fractalkine, is expressed by hepatocytes, HSCs, BECs and epithelial cells of the liver.[59,148] It can act as a free ligand in serum and promotes migration of immune cells, in particular monocytes.[149,150] In chronic hepatitis C, liver injury, and injured BECs, CX3CL1 expression is increased in intrahepatic cells.[60,151–155] This chemokine axis is responsible for the recruitment and accumulation of NK cells, which express CX3CR1, around injured bile ducts. In addition to pro-inflammatory effects, CX3CL1-CX3CR1 interactions mediate effects that protect the liver by preventing hepatocyte apoptosis, fibrosis, and activation of HSCs.[150,156,157]

Treg recruitment to the liver is mediated in large part by chemokines, many of which overlap with their effector counterparts allowing co-localization to sites of inflammation.[158] The explanted chronically inflamed livers in human transplantation contain Tregs that express CXCR3 at levels that are higher than those found in peripheral blood. Through CXCR3 and α4β1, these Tregs are able to bind and transmigrate through sinusoids under flow conditions. Additionally, Tregs that are derived from the liver express a tissue infiltrating phenotype with high levels of CXCR3, but low levels of CCR7. DCs in chronically inflamed livers also recruit Tregs through expression CCL17 and CCL22, two ligands of CCR4.[119] Once through the sinusoids, Tregs localize to bile ducts via interactions between CCR10 and CCL28 expressed on cholangiocytes. In HCV, expression of CCL28 is increased leading to increased infiltration of all subtypes of CCR10+ T cells, but with a predominance of Tregs.[134]

Other chemokine receptors expressed by naïve lymphocytes signal them to leave the liver, thus the loss of expression can lead to localization in infiltrated tissues. In particular, CCR7 expression on T cells allows for circulation out of liver through peripheral lymph nodes and secondary lymphoid tissue. CCR7 mediates this signaling by interacting with CCL19 and CCL21 as well as through L-selectin.[159] However, CCR7 expression in non-naïve lymphocytes has been observed in certain disease states. Many T cells in autoimmune and HCV hepatitis are CCR7+ and have the ability to migrate through the periphery, but are also CD62L-low and LFA-1 high, a phenotype that is characteristic of memory T cells.[159,160] These central memory cells are in contrast to effector memory T cells that do not express CCR7 and are therefore only localized to tissue.

Chemokine interactions also play an important role in recruiting non-lymphoid immune cells to the liver. CXCR2 expression directs neutrophils to sites of inflammation. When induced by LPS, neutrophils will migrate to the sinusoids and into tissue via CD44-hyalarunon interactions.[161] Diapedesis does not occur in post-sinusoidal epithelium due to the absence of the hyalarunon ligand.[162] Monocytes are recruited to inflamed livers by CX3CR1 and VAP-1.[149] CCR2 is an inducible chemokine receptor found on monocytes not expressed under homeostatic conditions that direct these cells to sites of inflammation.[163,164] Once directed to the liver, CCR2 expression keeps monocytes in hepatic tissue.[165] There is evidence that these monocytes differentiate into DCs that express CXCR1 and have the ability to produce TNFα, inducible nitric oxide synthase (iNOS), and IL-10 to mediate both pro- and anti-inflammatory processes[166,167] CCR8 has been implicated in liver inflammation and fibrosis; inhibition of it or its ligand CCL1 blocks differentiation of hepatic DCs and T cells protecting against injury.[168]

Gut-Liver Immune Axis

The liver and is bombarded with environmental, dietary, and bacterial antigens in the portal circulation. Intestinal and liver immunity are thus closely intertwined. First-line defense against pathogenic antigens is the gut mucosa that is coated with IgA and other anti-microbial substances.[169] Intestinal mucosa is also rich in lymphoid tissue from Peyer's patches and mucosal associated lymphatic tissue, which are rich in T cells, innate lymphoid cells, and gut associated dendritic cells.[52] LSECs, in turn, can imprint naïve lymphocytes with a gut-homing phenotype.[170] Mucosal memory T cells also preferentially recirculate through the liver and are not dependent on the expression of gut homing receptors, contributing to the liver's function as the main sentinel of the GI tract for the immune system.[171] The microbiome also contributes to gut immunity; alterations in microbiome homeostasis can lead to gut inflammation and in certain circumstances turn commensal organisms pathogenic.[172]

Intestinal immunity also uses chemokine signaling and adhesion molecules that are unique to the gut. CCL25 and α4β7 integrin secreted by small bowel epithelium interacts with CCR9 and MadCAM-1 to activate leukocytes, a mechanism that is confined to the intestine under normal conditions.[173,174] Lymphocytes are imprinted with a gut-homing phenotype by CD103+ DCs within lymphoid tissue and IL-7 by retinoic acid-dependent mechanisms. Down-regulation of CCR7 and L-selectin combined with upregulation of CCR9 and α4β7 leads to the loss of the ability to re-enter peripheral lymphoid tissue.[174] These DCs can also direct Tregs to the gut in the presence of TGF-β and IgA-producing B cells in the presence of IL-5 and IL-6. Tregs and B cells also interact with intestinal epithelium via CCR10-CCL28 interactions.[175–177]

Biliary epithelium is contiguous with intestinal mucosa and performs many of the same immune functions by similar mechanisms. Cholangiocytes normally express HLA class I molecules but not HLA class II and do not participate in antigen presentation. They are also an important source of IFNγ and TNFα.[129,178] Bile ducts secrete IgA antibody and express similar sets of TLRs to intestinal epithelium.[9] In response to cytokines and endotoxin, biliary epithelial cells (BECs) actively participate in leukocyte recruitment by upregulating

CXCL8, CX3CL1, CXCL12, and CXCL16.[58–61] These signals lead to upregulation of α4β1 to VCAM1 interactions. BECs can also upregulate CCL28 to recruit Tregs expressing CCR10 to the gut and liver.[134] Increase in bile duct expression of CXCL12 and CXC3L1 recruits Th17 cells and upregulates secretion of pro-inflammatory cytokines.[179–181]

IMMUNE CELL TRAFFICKING IN LIVER DISEASE

As described earlier, in homeostatic conditions, the liver is in a relatively anti-inflammatory state. The various liver APCs (LSECs, Kuppfer cells, DCs) are resistant to activation by the various antigens, including LPS, that bombard the liver constantly and in fact promote a regulatory environment.[182] This balance however, can be shifted to produce a physiologic immune response against pathogens. One such proposed mechanism is through the production of type 1 interferons (IFN-α/β). Viral infections of the liver promote synthesis of IFN-α/β by hepatocytes which in turn leads to recruitment of naïve T cells, increases production of IL-15, and promotes survival of CD8+ T cells.[183–186] Moreover, innate lymphocytes (e.g. NK & NKT cells) are relatively abundant in the liver compared to other tissues of the body. They have the ability to both recognize many other non-protein antigens produced by microorganisms, infected cells, and tumors and activate physiological immunity within the liver.[187]

The interactions of the gut and liver immune systems plays an important role in the pathophysiology of PSC. PSC is characterized by massive T-cell mediated inflammation of the portal tracts and bile ducts, leading to biliary strictures and eventually liver failure[152] There is a high incidence of PSC in patients with inflammatory bowel disease. Much of the T-cell recruitment is mediated by interactions between CCR9 on T cells and CCL25. Normally, expression of CCR9 is restricted to mucosal T cells in the intestine, while that of CCL25 is restricted to intestinal epithelium; this localization regulates recruitment of immune cells to the bowel.[174,188,189] CCR9-CCL25 interactions upregulate expression of MadCAM-1 in gut vessels and in turn increase adhesion of leukocytes expressing α4β7 integrins. However, in PSC, there is aberrant expression of CCL25 and MadCAM-1 on LSECs. A large proportion of liver effector T cells in PSC express CCR9 and α4β7 leading to inflammatory interactions within the liver that are normally localized to the intestine.[190,191]

Aberrant immune cell trafficking also underlies the pathology of PBC and autoimmune hepatitis. Antimitochondrial antibodies are present in almost all patients with PBC, with the E2 component of pyruvate dehydrogenase complex being the main autoantigen.[192–194] The large numbers of CD4+ T cells (both Tregs and Th17) that infiltrate portal tracts suggest cellular mechanisms play a large role in this disease's pathophysiology.[195] Studies of explanted livers from transplanted patients has shed light on the trafficking mechanisms at play. Chemokine receptors CXCR3 on LSECs and CCR4 ligands secreted by dendritic cells are involved recruiting T cells in autoimmune liver disease.[119] CX3CL1 is also upregulated by injured bile ducts, recruiting CX3CR1+ CD4 and CD8 T cells to portal tracts.[59] In advanced stages of autoimmune liver diseases, systemic levels of CXCL9 and CXCL10 are elevated but return to normal after successful treatment, suggesting that these signaling pathways are important mediators of pathologic inflmmation.[196]

Nonalcoholic fatty liver disease (NAFLD) is characterized by an aberrant increase in the accumulation of fat in the liver. Visceral fat, and particularly that in the liver, can produce an inflammatory response that can progress to non-alcoholic steatohepatitis (NASH).[197] This is an increasing cause of cirrhosis and liver failure in the world. In individuals who develop NASH, excessive free-fatty acids induce expression of Cyr61/CTGF/NOV (CCN1), a member of a family of extracellular matrix-associated signaling proteins. Its overexpression in the liver through TLR4 pathways leads to recruitment of myeloid-derived macrophages and subsequent severe inflammation.[198] Mouse models of NAFLD have revealed that both CCR2 and CD44 are also important mediators of leukocyte recruitment. Lack of CCR2 completely and CD44 partially reduces leukocyte recruitment, but this did not prevent the development of steatosis and inflammation, indicating there are redundant pathways of leukocyte recruitment produced by hepatic lipid accumulation.[199] On the other hand, blockade of CCL2, the ligand for CCR2 and CCR4 in another mouse model of steatohepatitis leads to a reduction of macrophage infiltration and inflammation in chronic hepatic injury.[200]

Infection with HCV exploits lymphocyte recruitment mechanisms to cause chronic inflammation and injury. HCV infection promotes differentiation of lymphocytes into a Th1 profile.[201,202] Increased CXCR3 and CCR5 levels are detectable in the periphery a few weeks after infection with a delayed infiltration of antigen-specific intrahepatic T cells detected 2–3 months later.[203,204] This recruitment is in part mediated by the upregulation of CXCL11 in infected hepatocytes.[204]HCV also induces increased expression of CXCL16 on BECs and portal endothelium, attracting CXCR6+ lymphocytes that contribute to chronic infection and inflammation.[61,120,205] The combination of serum CCL2 correlating with the severity of inflammation in HCV hepatitis and the enrichment of CCR2+ CD8 T cells in the inflamed liver suggests a role for the CCR2-CCL2 chemokine axis.[206] Modulation of host responses occurs via manipulation of promoter genes, such as that for CXCL8.[207] The impact HCV has on all these chemokine axes also leads to reduced effectiveness of the liver APCs to present antigen, allowing for viral survival.

Several chemokine axes have also been implicated in malignant conditions of the liver. In early studies of hepatocellular carcinoma (HCC), the CXCL12-CXCR4 axis had been identified as critical in the growth and progression of HCC.[208] In biopsies from HCC patients, there is higher expression in tumor tissue than in surrounding, non-cancerous liver.[209] There is also some evidence that the level of expression correlates to invasiveness, metastasis, and survival.[210,211] In contrast, other studies have shown that expression of CXCL12 and CXCR4 in HCC tissue lacks an association with survival.[212] CCL20-CCR6 is another pair of chemokines that are significantly upregulated in human HCC tumors.[213] This axis promotes growth of the hepatoma cell line Huh7 in *in vitro* experiments, suggesting CCL20-CCR6 interactions importance in tumor growth.[214] Additionally, CCL20 has been found to be overexpressed in colorectal liver metastatic lesions in humans, suggesting a role in spread of tumor.[215] Finally, CX3CL1-CX3CR1 interactions have also been implicated as an important part of immune responses against HCC.[216] Specifically CX3CL1 enhances anti-tumor effects of HCC in mice and high expression in serum of human patients is associated with a lower occurrence of metastasis.[217] Expression of the CCR5, CCR6, and CXCR3 in peripheral lymphocytes was reduced but higher (particularly CXCR3) in tumor

infiltrating cells of HCC patient, suggesting that these receptors are important in directing lymphocytes to malignancy in the liver.[218] Although these interactions described play some role in growth progression of liver tumors, the specific mechanisms by which these interactions mediate their effect remains unclear.

In liver transplantation, changes in immune cell trafficking are important in both ischemia/reperfusion (I/R) injury as well as in rejection. I/R injury results in oxidative liver damage and systemic inflammation. The initial inciting event seems to be damage to LSECs during cold preservation.[219] Once warm reperfusion takes place, KCs mediate early recruitment of leukocytes with later phases of injury mediated by neutrophil accumulation and CXC chemokine production.[220–222] These chemokines also mediate systemic injury; for example, CXCL2 has been observed to be a key mediator in I/R injury to the lungs in a rodent model of liver transplant.[223] DAMPS also serve as important mediators for immune cell trafficking in I/R injury. Formyl-peptide receptor 1, promotes neutrophil chemotaxis to transplanted liver grafts.[224] Matrix metalloproteinase 9 is also important for leukocyte migration by degrading ECM to allow for movement; this also produces ECM fragments that are highly chemotactic for other immune cells.[225,226] There are therefore multiple processes specific to reperfusion that mediate leukocyte trafficking and I/R injury in liver transplantation.

In the setting of graft dysfunction and liver rejection, immune cell trafficking has been well described. In the first week post-transplant higher serum levels of chemokines CCL2, CXCL8, CCL5, CXCL8, CXCL10 and IL-2R are associated with early allograft dysfunction. Pre-transplant, lower pre-operative IL-6 and higher IL-2R levels correlated with increased incidence and risk of early allograft dysfunction.[227] Graft dysfunction due specifically to acute cellular rejection also correlates with high CXCL9 and in particular to low CD44 levels.[228] On vascular and sinusoidal endothelium, CXCL9, CXCL10, and CXCL11 are highly upregulated in rejection, increasing interactions and recruitment of CXCR3+ B, NK, and CD4 T cells.[229–231] Rodent models of liver rejection have revealed that interactions between VCAM-1 on LSECs and α4β1 integrin on effector T cells are critical to adhesion and transmigration across PV endothelial cells.[232] CCL3 increases infiltration of recipient-derived NK and T cells.[229,233] CCL20-CCR6 have been detected at much higher levels in portal fields with significant increases in B cells and plasma cells, suggesting that axis' role in recruitment and promotion of humoral rejection processes.[230] CCR2 and CCR5 are involved with recruitment of infiltrating lymphocytes in acute and chronic rejection.[230] Other trafficking molecules that have been identified as important mediators in rejection include CCL2, CCL3L1, and CCL5.[234] Blockade of each of these pathways in multiple experimental models have ameliorated rejection, but no single one has completely eliminated alloimmune responses in liver transplantation.

POTENTIAL TARGETS OF THERAPY

As reviewed earlier, there are multiple redundant pathways and mechanisms that traffic immune cells to the liver in both homeostatic and pathologic conditions. Despite differences between the sinusoidal and non-hepatic vascular endothelium, no single receptor has been identified that directs immune cells only to the liver.[235] Instead, patterns of chemokine and adhesion molecule expression induce both pro- and anti-inflammatory responses. Multiple

animal models have been developed to explore modulation of trafficking for potential therapeutic applications. Transcriptional regulators, such as rosiglitazone, an agonist of PPAR-γ, reduces CXCL10 production as well as CCL2 and CCL20 in a mouse model of Crohn's Disease and PSC.[236–240] Antibodies have also been developed that target and neutralize specific chemokine receptors and ligands. Those against CXCL16 improve survival of mice with immune-mediated liver injury; against CXCL10 reduced hepatic fibrosis in chronic toxic liver injury; and those against CCL20 improved liver function tests, reduced expression of inflammatory and pro-fibrotic genes in a model of acute and chronic toxic liver injury.[241–243] Peptides that block chemokine receptors have also been developed; a recombinant analogue of CCL5 antagonizes CCR5 and CCR1, inhibiting HSC proliferation and reducing chemokine production and collagen deposition.[244] Inhibition of immune cell trafficking at multiple points has shown potential for therapeutic application in rodent models. Dual inhibition of CCR2 and CCR5 reduces recruitment of monocytes and macrophages, as well as HSC activation in rodent liver fibrosis, significantly reducing fibrosis and inflammation.[245] CXCR1 and CXCR2 antagonism also dramatically inhibits myeloid recruitment in a I/R rat model of transplantation, leading to decreased necrosis.[246]

A handful of pre-clinical models of trafficking blockade have been translated to clinical use. Blockade of CCR5 using the agent maraviroc has been applied to management of GvHD in hematopoietic stem-cell transplantation. A noncompetitive antagonist, maraviroc prevents CCL3, CCL4, and CCL5 binding and activation of signaling pathways.[247] It was initially developed for use in subtypes of human immunodeficiency virus (HIV) that used only CCR5 to enter cells.[248] In GvHD, this agent prevented of internalization of CCL5-blocked T-cell chemotaxis without impairing overall T-cell function or engraftment. This lead to a clinically significant reduction in both liver and gut GvHD.

Inflammatory bowel disease is another area where targeting leukocyte trafficking pathways has been applied. Vedolizumab and natalizumab are two monoclonal antibodies that have been used in refractory, severe forms of both Crohn's disease and ulcerative colitis.[249] Vedolizumab is specifically an antagonist for alpha4beta7, but not alpha4beta1. This prevents binding to MAdCAM-1 but not VCAM-1, thus exerting its anti-inflammatory effects in the gut without affecting leukocyte adhesion in other tissues.[250,251] Natalizumab is an alternative immune-modulating agent that targets the same pathway. It is a humanized IgG4 monoclonal antibody that binds to the alpha4 chains of integrins to inhibit translocation of leukocytes.[252] It antagonizes alpha4beta1 in addition to alpha4beta7 interactions; this non-specific binding has led to natalizumab's use as an agent for multiple sclerosis as well as inflammatory bowel disease.[253] Although these agents are effective in treating intestinal manifestations of Crohn's disease and ulcerative colitis, they fail to have any therapeutic effect in concomitant PSC.[254,255] Currently, there is an open label single arm study investigating anti-CXCL10 monoclonal antibodies' potential application in PBC patients.

Conclusions

As a main sentinel for the human immune system, multiple mechanisms have developed to signal immune cells to travel to the liver in both homeostatic and pathological conditions.

However, no one dominant signal exists that direct leukocytes to the liver, rather patterns of expression of multiple different signaling pathways are responsible. Although much has been revealed about these pathways, there remains much about the trafficking of pro-inflammatory and regulatory cells to be described. As with pathological conditions of other organ systems, there remains great potential to exploit these pathways for treating liver disease.

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Abbreviations:

APC	Antigen Presenting Cell
BEC	Biliary Epithelial Cell
CLEVER	Common Lymphatic Endothelial and Vascular Endothelial Receptor
DAMP	Damage Associated Molecular Patterns
DC	Dendritic Cells
GI	gastrointestinal
GvHD	Graft vs Host Disease
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antige
HSC	Hepatic Stellate Cell
ICAM	Intercellular Adhesion Molecule
I/R	Ischemia/Reperfusion
iNOS	inducible nitric oxide synthase
KC	Kupffer Cells
LFA	Lymphocyte Function-Associated Antigen
LPS	lipopolysaccharide

LSEC	Liver Sinusoidal Endothelial Cell
MadCAM	Mucosal Addressin Cell Adhesion Molecule
MHC	Major Histocompatibility Complex
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NK	Natural Killer
NKT	Natural Killer T
PAMP	Pathogen Associated Molecular Patterns
PBC	Primary Biliary Cirrhosis
PD	Programmed Death
PRR	Pattern Recognition Receptors
PSC	Primary Sclerosing Cholangitis
Th	Helpter T cell
Treg	Regulatory T cell
TLR	Toll-like Receptors
VAP	Vascular Adhesion Protein
VCAM	Vascular Cell Adhesion Molecule

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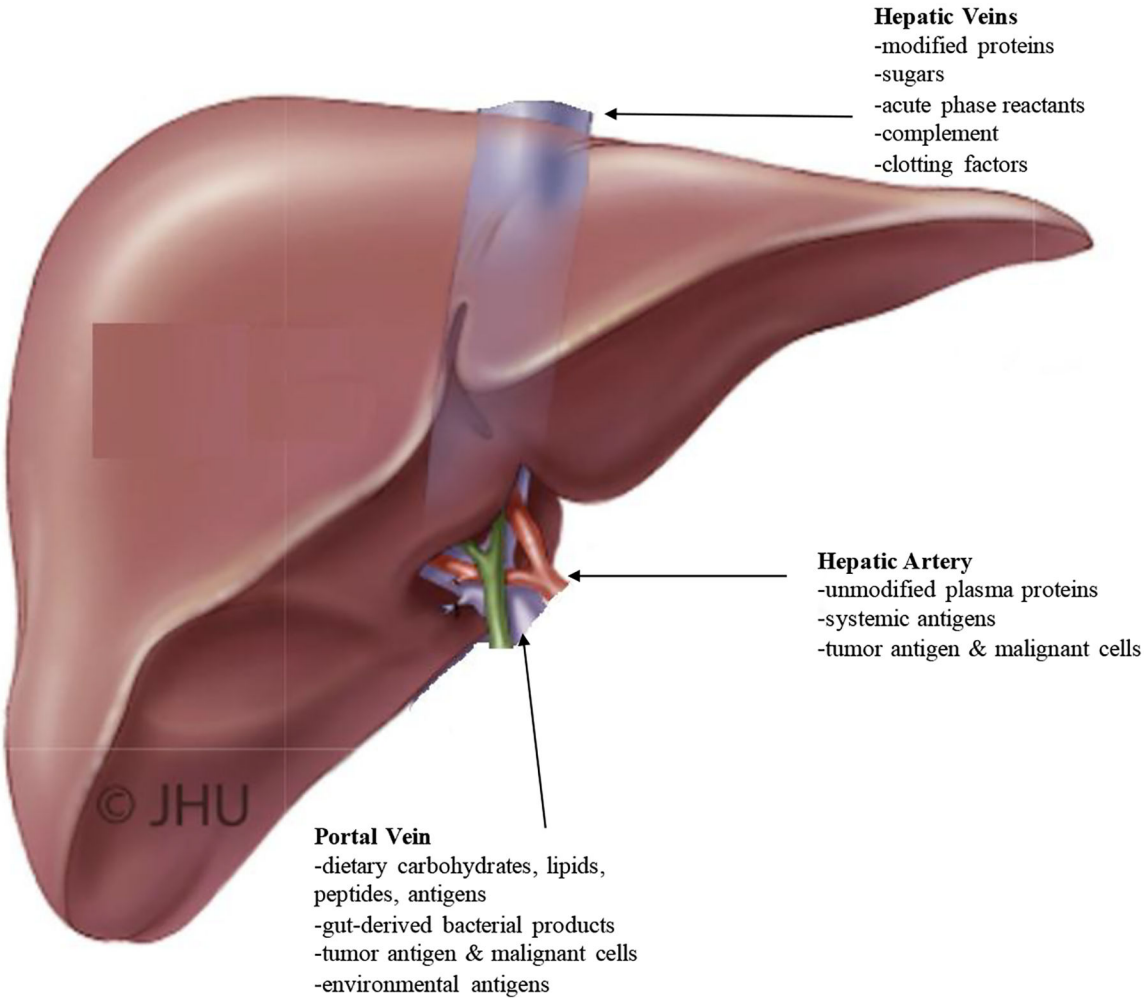

Figure 1:

Blood Circulation to the Liver: The possesses a unique dual circulation, receiving blood both from the systemic arterial system via the hepatic artery and from the mesenteric system via the portal vein. This arrangement allows the liver to monitor and process substrates from both areas of the body and to release appropriate products systemically. Adapted with permission from *Current Surgical Therapy, 12th Edition p. 393*.

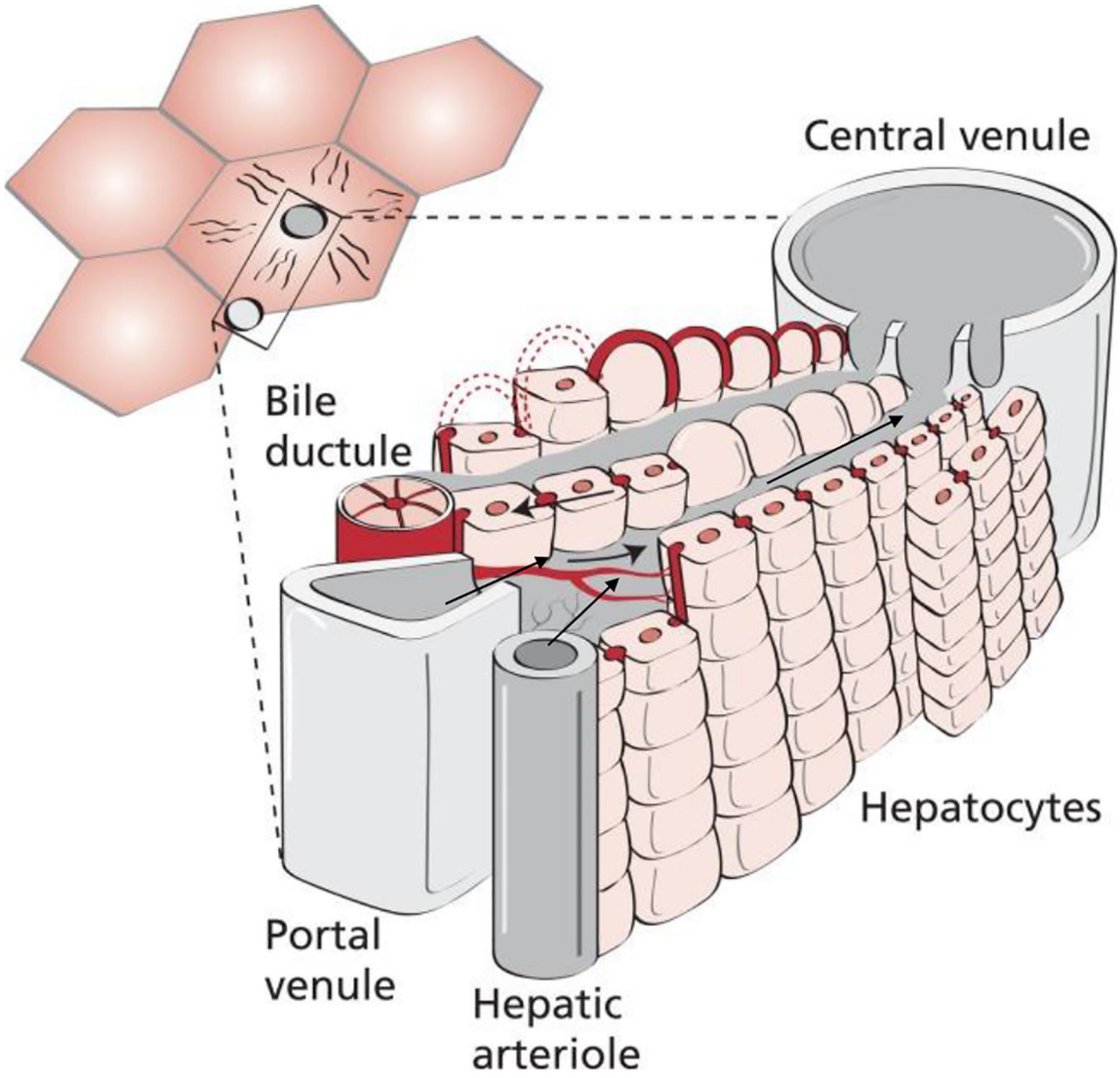

Figure 2:

Microcirculation of hepatic lobule. Terminal branches of the hepatic artery and portal vein both drain into liver sinusoids where blood is then carried to the central vein, a branch of the hepatic vein. Multiple sets of hepatic artery and portal vein branches drain into a single central vein. Adapted with permission from *Juza et al. Clin Anat 2014;27(5):764–769.*[256]

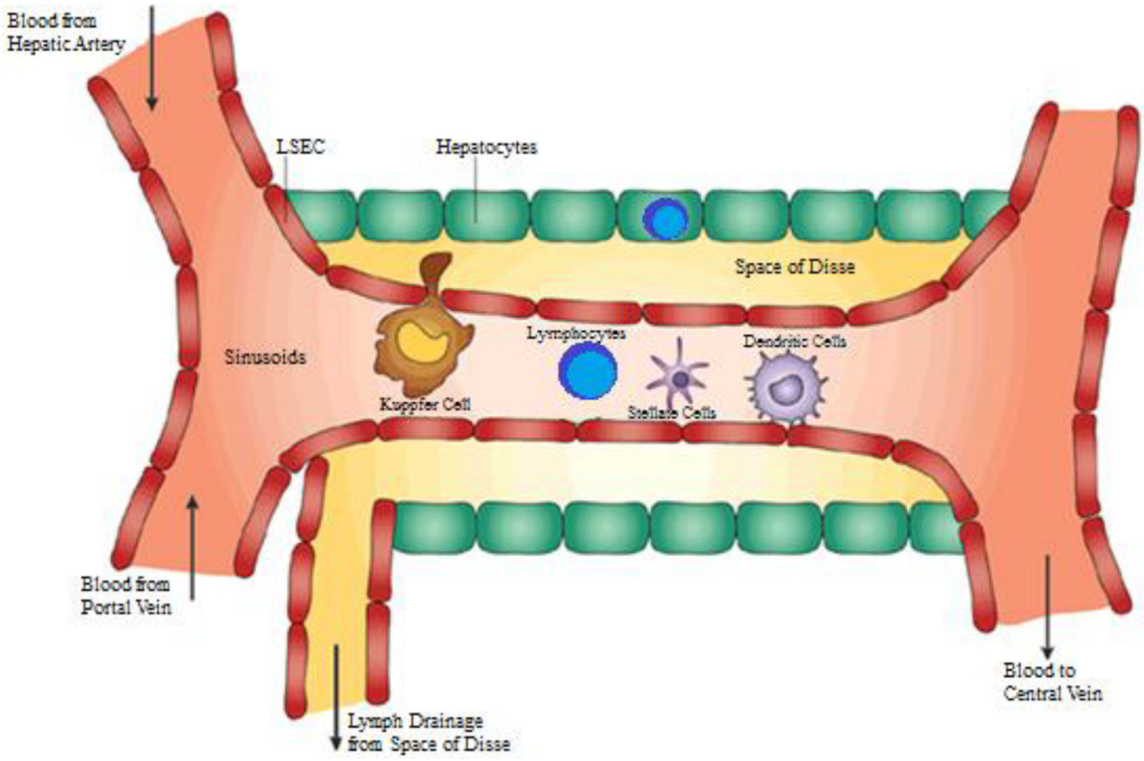

Figure 3.

Resident Immune Cells within Liver. The liver is home to cells with a diversity of immunologic functions. Antigens from systemic and portal circulation are carried into the sinusoids where they are met by resident KCs, lymphocytes, dendritic cells, and HSCs. LSECs line the sinusoids and can also present antigens to activate the immune system. Within the sinusoids are fenestrations where antigens can extrude into the Space of Disse and also through which hepatocytes can sample antigens within sinusoidal lumen. Lymphocytes also reside within the parenchyma amongst hepatocytes. Adapted from with permission from *Crispe, Nat Rev Immunol, 2003;3(1):51–62*.

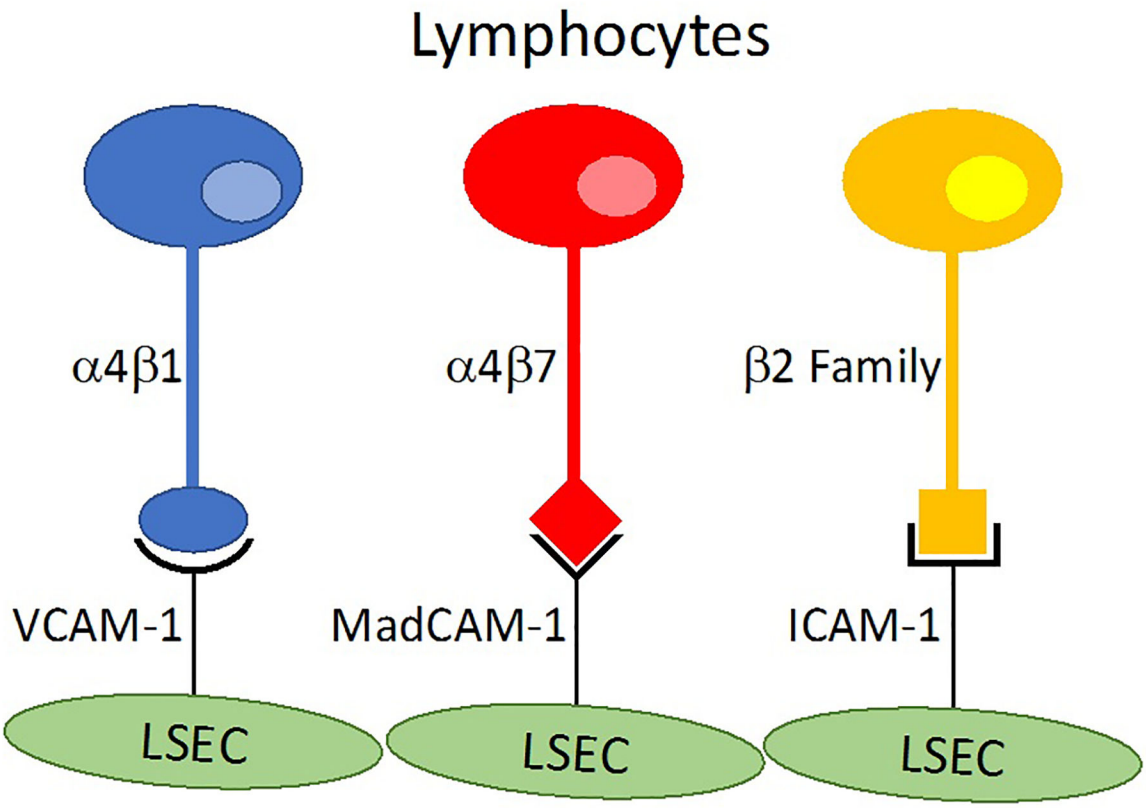

Figure 4.

A schematic representation of adhesion molecules within liver sinusoids. LSECs express a number of adhesion molecules, including VCAM-1, MadCAM-1, and ICAM-1 that bind to the integrins α4β1, α4β7, and the β2 family. VCAM-1 is expressed at levels within sinusoids that other tissues only express under inflammatory conditions. ICAM-1 is also expressed by LSECs at levels that are normally seen in post-capillary venules. MadCAM-1 is normally only expressed in the gut, directing immune cells to the intestine; however, this becomes an important mediator in PSC when aberrantly expressed by LSECs. ICAM-1 is expressed on the basal membrane, whereas VCAM-1 and MadCAM-1 are expressed on the luminal membrane.

Table 1.

Chemokine Receptors and Ligands in Immune Cell Trafficking

Receptor	Chemokine	Distribution of Interactions	Trafficking in Liver
CC subgroup			
CCR1	**CCL3, CCL5, CCL7, CCL8, CCL13–16**	**monocyte, effector & memory T cell recruitment**	
CCR2	**CCL2, CCL7, CCL8, CCL13**	**monocyte, effector & memory T cells, Th1 recruitment**	
CCR3	CCL5, CCL7, CCL11, CCL15–16, CCL24, CCL26	Th2 recruitment	
CCR4	CCL17, CCL22	Th17, Th2, Treg recruitment and retention	
CCR5	**CCL3, CCL4, CCL5, CCL8**	**Th1, monocyte recruitment**	**portal veins and venules**
CCR6	CCL20	all subtypes of T cells, B cell recruitment	malignancy
CCR7	CCL19, CCL21	recruitment to secondary lymphoid tissue	periportal lymph nodes
CCR8	CCL1	Th2, monocyte recruitment	
CCR9	**CCL25**	**recruitment to GI tract**	**sinusoids in PSC**
CCR10	CCL25, CCL28	recruitment to GI tract	bile ducts
CXC subgroup			
CXCR1	CXCL6, CXCL7, CXCL8	neutrophil, monocyte recruitment	
CXCR2	CXCL1–3, CXCL5–8	neutrophil, monocyte recruitment	
CXCR3	**CXCL9–11**	**Th1, Th17, Treg recruitment**	**sinusoids in non-specific liver inflammation**
CXCR4	CXCL12	B cell recruitment	sinusoids and bile ducts; HCC
CXCR5	CXCL13	B cell recruitment	
CXCR6	**CXCL16**	**NK and T cell recruitment**	**sinusoids and biliary epithelium**
CX3CR1	**CX3CL1**	**monocyte and NK cell recruitment**	**biliary epithelium in PBC**