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REVIEW

Lymphocyte recruitment and homing to the liver in primary biliary cirrhosis and primary sclerosing cholangitis

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Abstract The mechanisms operating in lymphocyte recruitment and homing to liver are reviewed. A literature review was performed on primary biliary cirrhosis (PBC), progressive sclerosing cholangitis (PSC), and homing mechanisms; a total of 130 papers were selected for discussion. Available data suggest that in addition to a specific role for CCL25 in PSC, the CC chemokines CCL21 and CCL28 and the CXC chemokines CXCL9 and CXCL10 are involved in the recruitment of T lymphocytes into the portal tract in PBC and PSC. Once entering the liver, lymphocytes localize to bile duct and retain by the combinatorial or sequential action of CXCL12, CXCL16, CX3CL1, and CCL28 and possibly CXCL9 and CXCL10. The relative importance of these chemokines in the recruitment or the retention of lymphocytes around the bile ducts remains unclear. The available data remain limited but underscore the importance of recruitment and homing.

Keywords Lymphocyte homing · Mucosal addressin cellular adhesion molecule-1/MAdCAM-1 · Chemokines · Primary biliary cirrhosis · Primary sclerosing cholangitis

Introduction

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases characterized by progressive destruction of bile ducts. Whereas PBC affects the small intrahepatic bile ducts, PSC involves the intra- and/or extrahepatic bile ducts. PBC is an organ-specific autoimmune disease with female predominance, genetic predisposition, high titer serum anti-mitochondrial autoantibodies, disease-specific antinuclear autoantibodies, frequent association with other autoimmune diseases, and strong indications that the destruction of small bile ducts is autoimmune-mediated [1]. PSC shares many of these features including *p*-ANCA autoantibodies in up to 80% of patients, genetic predisposition, and association with other autoimmune diseases. In particular, there is a link between inflammatory bowel disease (IBD), with >70% of PSC patients having IBD, most frequently ulcerative colitis, at some point during their lives. Nonetheless, PSC differs from classical autoimmune diseases in male rather than female predominance and is poorly responsive to immunosuppressive treatment. In addition, there is only circumstantial evidence that bile duct destruction in PSC is an immune-mediated response to an autoantigen [2, 3].

Both PBC and PSC are characterized by massive infiltration of T cells into the portal tract, the infiltrate consisting predominantly of T cells [4-7]. For reviews and discussion on the immunobiology of PBC, including generic mechanisms of autoimmunity, we refer to several recent and key publications [8-22].

In PBC liver compared to peripheral blood, there is a 100-fold enrichment of CD4+ T cells and a 10-fold enrichment of CD8+ T cells specific for the major PBC autoantigen, strongly suggesting that both populations participate in the bile duct injury seen in PBC [1]. In keeping with a major role for cellular immune mechanisms in PBC, there is type-1 cytokine predominance in serum and liver of PBC patients [23, 24]. Very little is known

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about the contribution of T cells to the lesions of PSC and the cytokine milieu in PSC liver, except that liver-infiltrating lymphocytes (LIL) from PSC patients produce significantly increased amounts of TNFα and IL-1β but decreased levels of IFNγ [7].

According to the general paradigm, leukocyte extravasation is a complex multistep process that begins with "tethering" and rolling of blood-born leukocytes, i.e., reversible and transient interactions mediated mainly by selectins. This slows down the immune cells sufficiently to allow them to interact with chemokines presented by endothelial cells. These can then increase the affinity and avidity of leukocyte integrins for their endothelial adhesion molecule receptors, thereby allowing firm adhesion to occur. The adhesion molecules involved in firm attachment frequently belong to the immunoglobulin superfamily, which includes intercellular adhesion molecules (ICAM)-1–5, vascular cell adhesion molecule 1 (VCAM-1), and mucosal addressin cellular adhesion molecule 1 (MAdCAM-1). Firm adhesion is a prerequisite for subsequent transendothelial migration into the tissue. Once lymphocytes have entered a specific tissue, they follow sequential and combinatorial chemotactic gradients to their final destination.

Chemokines play an essential role at every step of this adhesion cascade and subsequent migration. They do so by increasing the affinity and avidity of integrins for their adhesion molecules, providing chemotactic signals for transendothelial migration and the subsequent migration to specific compartments within a tissue and by triggering integrin activation required for the binding to adhesion and cell-matrix molecules involved in tissue retention. They are divided into four subfamilies (CC, CXC, C, and CX3C, with CC and CXC chemokines representing the largest group) based on the arrangement of the first two of four conserved cysteine residues. They can be further subdivided functionally into homeostatic and inflammatory chemokines (see Table 1 for the nomenclature and receptor usage of inflammatory cytokines). Inflammatory chemokines are induced or upregulated during inflammation and mediate leukocyte recruitment; homeostatic chemokines are constitutively expressed and regulate navigation of leukocyte precursors during hematopoiesis and of mature lymphocytes in secondary lymphoid tissue [25]. Note, however, that some chemokines (e.g., CCL21) do not neatly fit into one of these categories.

There is increasing evidence that chemokines do not establish soluble chemokine gradients at the luminal endothelial surface but instead are immobilized via attachment to specific glycosaminoglycans [26, 27]. Therefore, the production of specific glycosaminoglycans by endothelial cells may represent mechanisms to provide tissue-specific recruitment signals [26, 27]. In addition, although endothelial cells can produce many chemokines, themselves, they are also able to take up, transcytose and then present chemokines produced by surrounding cells [27, 28].

Chemokines exert their effects through binding to seven-membrane-spanning G-protein coupled receptors expressed on leukocyte and lymphocyte subsets. Frequently, a certain chemokine can bind to several different receptors; conversely, a receptor can be shared by several chemokines. There is extensive cross-talk between chemokines on numerous levels, e.g., through downregulation of shared receptors [29], enhancing the surface density of unrelated receptors [30] or through blocking of signaling events downstream from receptor activation [31].

Naïve lymphocytes recirculate between blood and peripheral lymph nodes. During this stage, they express L-selectin and CCR7, which allow them to enter lymph nodes which express the L-selectin ligand peripheral lymph node addressin (PNad) and the CCR7 ligands, CCL19 and CCL21. Once lymphocytes encounter their cognate antigen, they generally downregulate CCR7 and L-selectin expression and instead acquire a different set of adhesion receptors that allow them to be recruited to sites of inflammation and/or to "home," i.e., to preferentially return to the tissue in which they were originally activated. Recruitment and homing to certain tissues has been shown to involve the recognition of specific "addressins," i.e., tissue-specific ligands expressed by vascular endothelial cells, by homing receptors expressed on the lymphocyte. A further level of specificity is provided by chemokine receptor pairings. For example, homing to the gut is mediated by α4β7 integrin on lymphocytes binding to mucosal MAdCAM-1. The chemokine CCL25, which is capable of activating α4β7, is expressed preferentially in the small intestine, where it interacts with lymphocytes expressing its cognate receptor CCR9. Skin homing involves interactions between cutaneous lymphocyte antigen with E-selectin and CCL17 with CCR4. No specific addressin has been identified for the liver.

A unique feature of the liver is its dual blood supply, with arterial blood entering via the hepatic arteries and venous blood coming from the gut via the portal veins. Hepatic arterioles and portal venules transport arterial and venous blood into the sinusoids, which then take it through the lobule to the central vein. Lymphocytes can enter the liver at several sites, the most important probably being the portal vessels and the sinusoids. Portal veins constitutively express low levels of ICAM-1 and occasionally ICAM-2 and VCAM-1 [32-35]. E-selectin is generally not detectable [32, 36], whereas P-selectin may be weakly expressed on some portal vein endothelia [32]. Lymphocyte extravasation at this site is thought to proceed according to the general paradigm.

Table 1 Chemokines, their official and common names, and their receptors

Official nomenclature	Common name	Abbreviation	Receptor
CCL2	Monocyte chemoattractant protein-1	MCP-1	CCR2, CCR4, CCR9
CCL3	Macrophage inflammatory protein-1α	MIP-1α	CCR1, CCR5
CCL4	Macrophage inflammatory protein-1β	MIP-1β	CCR5, CCR9
CCL5	Regulated upon activation normal T l		CCR1, CCR3, CCR5, CCR9
CCL20	Macrophage inflammatory protein-3α, Liver and activation regulated chemokine	MIP-3α,	
LARC	CCR6		
CCL21	Secondary lymphoid chemokine	SLC	CCR7
CCL25	Thymus-expressed chemokine	TECK	CCR9
CCL28			CCR10
CXCL9	Monokine induced by IFNγ	MIG	CXCR3
CXCL10		IP-10	CXCR3
CXCL11	IFN-inducible T cell a chemoattractant	I-TAC	CXCR3
CXCL12	Stromal (cell)-derived factor-1	SDF-1	CXCR4
CXCL16			CXCR6
CX3CL1	Fractalkine		CX3CR1

Sinusoidal endothelium constitutively expresses ICAM-1 [32, 37] and ICAM-2 [32], whereas levels of VCAM-1 and E-selectin are minimal or undetectable [32, 36]. Note, however, that constitutive expression of E-selectin has been reported on cultured hepatic sinusoidal endothelial cells (HSEC) [38]. Lymphocyte recruitment in the sinusoids does not involve the classical tethering and rolling step in cultured human [39] or mice HSEC [40]. Instead, the vast majority of lymphocytes immediately arrest. This is thought to be due to the low to undetectable levels of sinusoidal selectin expression, which seems to be dispensable in the low-shear environment of the sinusoids. There are indications that vascular adhesion protein 1 (VAP-1) plays a particularly important role in lymphocyte extravasation in the sinusoids.

Adhesion molecules in PBC and PSC

VAP-1

Unlike most other adhesion molecules, VAP-1 does not belong to the selectin, integrin, or immunoglobulin super families but is a syaloglycoprotein and copper-containing semicarbazide-sensitive amine oxidase that exists in both membrane-bound and soluble forms [41]. It mediates sialic-acid-dependent adhesion of lymphocytes to peripheral lymph node high endothelial venules (HEV) [42] and promotes shear-dependent lymphocyte adhesion to, and transmigration across, hepatic sinusoidal endothelium in vitro [39, 43, 44]. Both its adhesive function and enzyme activity contribute to these processes [38, 39, 45]. In addition, VAP-1 has been shown to activate hepatic endothelial cells, resulting in the upregulation of E-selectin, P-selectin, ICAM-1 transcription and translation, and enhanced production of CXCL8 (IL-8), thereby increasing lymphocyte adhesion [46, 47]. The lymphocyte ligand of VAP-1 has not been identified. From available data, it also remains unclear at which step of the adhesion cascade VAP-1 comes into play. Studies with isolated hepatic sinusoidal endothelial cells suggest that it mediates firm adhesion but does not affect lymphocyte rolling [47], whereas the results obtained with liver sections point to a role in the early tethering interactions [43, 44]. Recent data obtained with VAP-1 expressing rabbit heart endothelial cells suggest that VAP-1 functions after the initial tethering step [45]. VAP-1 can use primary amine groups on the surface of lymphocytes as a substrate. During the reaction, a transient covalent bond is formed between the endothelial VAP-1 and the lymphocyte. This comes into play after the initial tethering and reduces the rolling velocity, thereby providing time for the chemokine-mediated integrin activation that is a prerequisite for firm adhesion.

In humans, VAP-1 is constitutively expressed in endothelial cells of several organs and tissues, with the greatest abundance found in high endothelial venules of peripheral lymph nodes. Hepatic vascular and sinusoidal endothelium, but not bile ducts or hepatocytes, also express low constitutive levels of this protein [43, 44]. Inflammation or inflammatory mediators can induce VAP-1 in a tissue-specific manner [48, 49]. However, data from a very limited number of patients with acute liver allograft rejection or PBC

suggest that inflammation does not enhance VAP-1 expression in portal and sinusoidal endothelium or induce it in other cell types since both the pattern and intensity of VAP-1 immunoreactivity were the same in normal and diseased livers [43] (see also Table 2). Consistent with these observations, cultured HSEC were found to constitutively produce low levels of VAP-1, which were not enhanced by incubation with TNFα, IL-1β, IFNγ, bile acids, or LPS [39]. All of these agents (with the exception of bile acids which were not tested) can enhance VAP-1 expression in certain other tissues in an organ- and cell type-specific manner [49].

Of particular note, there are indications that VAP-1 in human peripheral lymph nodes has marked lymphocyte subset selectivity, mediating shear-resistant adhesion of CD8+ T cells and NK cells but binding CD4+ T cells poorly [42, 50]. Whether VAP-1 on hepatic endothelium is equally subset-specific has not been investigated. Furthermore, in mice, VAP-1 selectively mediates the hepatic recruitment of Th2 cells, whereas Th1 cells used α4β1 integrin [51]. However, in vitro generated Th1 and Th2 cells, as used in this study, frequently do not adequately reproduce the behavior of their in vivo counterparts [52, 53]. In view of the importance of Th1 and CD8+ T cells in PBC and possibly PSC, it would be interesting to establish the relevance of these findings and also their pertinence to human liver.

ICAM-1 and VCAM-1

In normal human liver, there is constitutive, though weak expression of ICAM-1 on sinusoidal endothelium, still weaker or even undetectable levels have been reported on portal endothelium [32-34, 37], and no staining has been detected on bile ducts. Immunoreactivity for VCAM-1, if at all detectable, is generally confined to the portal endothelium in normal liver [32-34, 54]. Note, however, that in primary culture, both human biliary epithelial cells (BEC) and HSEC constitutively express low levels of ICAM-1, whereas VCAM-1 is not always detectable [39, 55]. As is seen in numerous other endothelial and epithelial cell types, expression of ICAM-1 is enhanced and that of VCAM-1 induced or upregulated by incubation with inflammatory cytokines (TNFα or IL-1β) or IFNγ.

In PBC and PSC, ICAM-1 and VCAM-1 are induced or upregulated on portal and sinusoidal endothelium [34, 35, 37, 56] (see also Table 2). This upregulation of ICAM-1 and VCAM-1 is not only applied to PBC and PSC but is also seen in other inflammatory liver diseases, including acute and chronic rejection and viral hepatitis [32, 33, 57], although there are some indications that the pattern is somewhat disease-specific [58]. However, upregulation of ICAM-1 expression on bile ducts seems to be quite specific for PBC, PSC, and other liver diseases in which bile ducts are the major targets of immune-mediated destruction [32, 34, 35, 59, 60]. VCAM-1 is only very occasionally detected on bile ducts of PBC and PSC patients [34, 35]. Note, however, that immunoreactivity for ICAM-1 on bile ducts and ductules is detected in some but not all patients with PSC and PBC [34, 35, 37, 61]. Both its presence and its distribution seem to depend on the disease stage since it is seen almost exclusively in more advanced disease [35]. This suggests that ICAM-1 induction or upregulation is a consequence rather than a cause of bile duct inflammation. Lymphocytes expressing the ICAM-1 ligand, LFA-1, are seen only occasionally in normal liver, and their frequency is greatly increased in various liver diseases [33, 34, 58]. Unlike hepatocellular liver diseases, LFA-1+ T cells are found mostly around damaged bile ducts in the vicinity of ICAM-1-expressing BEC [37, 61]. This indicates that upregulation of biliary ICAM-1 can result in enhanced lymphocyte recruitment to bile ducts.

MAdCAM-1 and the aberrant homing of mucosal lymphocytes to PSC liver

There is a strong link between PSC and IBD, and certain molecules involved in lymphocyte recruitment are shared between the gut and the liver. This is thought to be part of an enterohepatic lymphocyte recirculation that allows for immune surveillance across both liver and gut, which encounter some of the same antigens due to their connection via the portal circulation. This prompted Grant et al. [62] to formulate the hypothesis that PSC is mediated by long-lived memory T cells that were originally activated in the gut and are recruited to the liver due to aberrant inflammation-induced expression of adhesion molecules

Table 2 Changes in adhesion molecule expression in PBC and PSC

Adhesion molecule	Portal vein			Sinusoidal EC			Bile ducts		
	normal	PBC	PSC	Normal	PBC	PSC	Normal	PBC	PSC
ICAM-1	−/(+)	++	++	+	++	++	−	−/+	−/+
VCAM-1	−/(+)	++	++		++	++	−	−/(+)	−/(+)
VAP-1	+	+	+	+	+	+	−	−	−
MAdCAM-1	−	+	+	−	+	+	−	−	−

"*−/(+)*" negative or occasionally weakly positive. "−/+" negative in some, positive in other patients

and chemokines that are usually restricted to the gut. When these cells become activated in the liver by cross-reactive self-antigens in the liver or by gut antigens that have entered the liver via the portal vein, the inflammatory response may become exaggerated and, if prolonged, result in chronic inflammation.

Several lines of evidence support this hypothesis. Under normal conditions, the mucosal vessels of the gut are essentially the only site of MAdCAM-1 expression in humans [63]. However, this adhesion molecule, while not detected in normal liver, can be expressed by hepatic endothelium of patients with chronic inflammatory liver disease [64, 65]. Discussions of the role that aberrant homing of mucosal lymphocytes plays in the pathogenesis of the hepatic complications of IBD underscores the importance of MAdCAM-1 expression in inflammatory liver diseases "associated with IBD" [62, 66, 67]. However, this statement is somewhat incomplete. In one of the only two existing studies on the expression of this adhesion molecule in human liver diseases, Hillan et al. [65] detected MAdCAM-1 expression in association with portal tract inflammation, whether due to hepatitis B or C, PBC, or PSC. In particular, portal vessels and lymphoid aggregates stained positive, and this is similar to the results reported by Grant et al. [64], who detected some additional staining of the sinusoids. However, the proportions of specimens positive for MAdCAM-1 differed between the studies. Grant et al. [64] reported that the majority of specimens from PSC and autoimmune hepatitis (AIH) patients (88% and 70%), but only 64% of PBC and 14% of chronic rejection specimens, showed immunoreactivity. In contrast, 71% of needle biopsy samples from PBC patients, but only 20% of specimens of PSC patients, were positive for MAdCAM-1 in the investigation by Hillan et al. [65]. However, in that study, all explanted liver samples from PBC and PSC patients demonstrated immunoreactivity for this adhesion molecule. This may simply reflect the focal nature of MAdCAM-1 expression, limiting the detection in small biopsy samples. It could indicate, however, that MAdCAM-1 is increasingly upregulated with disease progression and that could suggest that expression of this adhesion molecule is a consequence rather than a cause of inflammation. In order to clarify the true extent of MAdCAM-1 expression and its relation to the disease stages in PSC and PBC, further investigations are clearly needed.

In a study of nine PSC patients, the MAdCAM-1 ligand, $\alpha4\beta7$ integrin, was expressed on LIL from seven with 10% and 50% of infiltrating lymphocytes in portal tracts staining positive for $\alpha4\beta7$ expression compared to <10% of lymphocytes in PBC samples [5]. Grant et al. [64], themselves, reported that only ~10% of LIL in PSC expressed $\alpha4\beta7$ compared to ~40% of PBL from the same patients. However, PSC liver contains a higher proportion of $\alpha E\beta7$+ T cells compared to peripheral blood, and $\alpha4\beta7$ T cells have been reported to differentiate within tissue into $\alpha E\beta7$+ cells. Unfortunately, LIL from PBC or AIH patients were not analyzed by flow cytometry, even though immunohistochemistry reveals that a proportion of intrahepatic lymphocytes in all liver diseases studied were positive for $\alpha4\beta7$. Further studies are called for in order to resolve the question whether $\alpha4\beta7$ expression characterizes mainly LIL in PSC or pertains to essentially all liver diseases.

Chemokines in PBC and PSC

Chemokines that can trigger $\alpha4\beta7$-mediated binding to MAdCAM-1

CCL25 Interactions between the gut-specific chemokine CCL25 with its receptor CCR9 results in activation of the $\alpha4\beta7$ integrin, thereby allowing firm adhesion of lymphocytes to MAdCAM-1 [68]. Note, however, that it did not trigger the shape changes associated with motility and transendothelial migration. In addition to the MAdCAM-1–$\alpha4\beta7$ pairing, this provides another level of specificity in the gut homing of lymphocytes. Analysis of CCL25 and CCR9 expression in various liver diseases indicates that CCL25 immunoreactivity, detected mainly on sinusoidal endothelium in areas of interface hepatitis, was highly specific for PSC since it was not seen in PBC and other inflammatory liver diseases [69] (see also Table 3). CCR9 was detected on 20% of LIL in PSC where it was frequently co-expressed with $\alpha4\beta7$ while <2% of LIL were CCR9 positive in other liver diseases. Although these results await independent confirmation, they strongly suggest that the MAdCAM-1/$\alpha4\beta7$/CCL25/CCR9 axis plays a specific role in the pathogenesis of PSC but not in PBC and other inflammatory liver diseases. They also provide further support for the hypothesis that PSC involves aberrant homing of mucosal lymphocytes to the liver. Note, however, that CCR9+ lymphocytes are found almost exclusively in the small intestine, whereas few are detected in the colon [70]. Similarly, CCL25 is specifically expressed in the small intestine and not in the colon. Therefore, one would expect PSC to be associated mainly with Crohn′s disease, which affects the entire gut, but not with ulcerative colitis, affecting only the colon. For as yet unknown reasons, the opposite is the case. However, it is interesting that the ulcerative colitis associated with PSC has a unique phenotype in which there is ileal involvement and rectal sparing [71]. An understanding of the factors that induce the expression of CCL25 in liver and intestine may shed some light on this paradox but remains elusive.

Table 3 Changes in chemokine expression in PBC and PSC

Chemokine	Portal vein			Sinusoidal EC			Bile ducts		
	normal	PBC	PSC	normal	PBC	PSC	Normal	PBC	PSC
IP-10	−	+ (?)	ND	−/+	ND	ND	−	+	ND
MIG	−/+	+ (?)	ND	−/+	ND	ND	−	+	ND
ITAC	−	ND	ND	+	ND	ND	ND	ND	ND
CCL21									
CCL25	−	−	−	−	−	++	−	−	−
CCL28	−	+	+	−	−	−	−	++	++
CXCL12 (SDF-1)	−	−	−	−	−	−	+	++	++
CXCL16	+	+	+	+	+	+	+	++	++
CX3CL1 (fractalkine)	+	+	+	−	−	−	(+)	++	(+)

ND not determined; "−" negative; "*(+)*" faint; "−/+" nondetectable in some, weakly positive in others; "+" clearly detectable; "++" strong staining

CCL21 If aberrant expression of MAdCAM-1/α4β7 integrin and CCL25/CCR9 are specifically involved in the recruitment of lymphocytes to liver diseases associated with IBD, the question then arises as to what, if any, function MAdCAM-1 expression has in PBC and other hepatic diseases. In this context, it is interesting to note that not only CCL25 but also CCL21, CCL28, and CXCL12 are capable of triggering α4β7-mediated adhesion of human PBL to MAdCAM-1 under shear stress in vitro [68, 72, 73]. Therefore, whether these chemokines play a role in the recruitment of T lymphocytes to PBC liver via MAdCAM-1 will depend on the actual number of α4β7-positive lymphocytes that enter the liver. CCL21 is a chemokine usually expressed on HEV in peripheral lymph nodes and Peyer's patches, and its ability to activate the α4β7 integrin-mediated adhesion of lymphocytes to MAdCAM-1 [68, 72] plays an important role in the recruitment of naïve lymphocytes to Peyer's patches. In addition, CCL21 can also trigger the shape changes that precede transendothelial migration and can activate α4β1 integrin-mediated lymphocyte binding to VCAM-1 under fluid flow [68].

A characteristic of PSC, PBC, and a variety not only of other autoimmune disease but also of chronic hepatitis C (CHC) is the presence of lymphocyte aggregates in the target organ. These organize into lymphoid follicles that contain HEV expressing either PNAd or MAdCAM-1 [64]. In mice, ectopic expression of CCL21 results in lymphoid neogenesis [74, 75]; the presence of CCL21 is sufficient to trigger integrin-dependent adhesion of naïve lymphocytes to nonlymphoid tissue and to induce their extravasation [76]. In human autoimmune diseases such as ulcerative colitis or rheumatoid arthritis, the lymphoid neogenesis is associated with expression of CCL21 mRNA in endothelial cells, including the HEV within the lymphoid follicles as well as blood vessels outside these organized lymphoid structures [76].

CCL21 is restricted to a few small lymphatic vessels in normal liver but is expressed in portal tracts in PSC and PBC, particularly in lymphoid aggregates [77]. The strongest immunoreactivity is seen on vascular endothelium of vessels exhibiting the morphology of HEV. Lymphoid aggregates in PBC; PSC and other liver diseases also demonstrated MAdCAM-1 immunoreactivity, and some vessels with HEV morphology within these aggregates are occasionally positive for MAdCAM-1 staining [64, 65]. This suggests a functional role for CCL21 in the recruitment of CCR7+ lymphocytes to the lymphoid aggregates within PBC and PSC portal tracts. CCR7, the receptor for CCL21, was expressed on a significantly higher percentage of PBL (76% vs. 50%) and intrahepatic T cells (20% vs. 9%) from PSC and PBC patients compared to healthy controls [77]. Of note, a high proportion of LIL in PSC were CD45RA+, and not all could be characterized as primed T cells that had reverted to a CD45RA+ phenotype. This suggests that CCL21 plays a role in the recruitment of naïve T cells to the liver, which would be consistent with the observation that murine CCL21 can recruit naïve T lymphocytes to nonlymphoid tissues [76]. Together, these results support the hypothesis that lymphoid neogenesis provides an environment for interactions between immune cells and antigen-presenting cells within the peripheral tissue that represents the antigen source [75] and, therefore, a site where autoreactive naïve T cells may be primed directly at the site of inflammation [76].

CCL28 Like CCL25 and CCL21, CCL28 can trigger α4β7-mediated adhesion of human PBL to MAdCAM-1 as well as α4β1-mediated binding to VCAM-1 under shear stress in vitro [68, 72, 73]. It also induces transwell chemotaxis of PBL and LIL [78]. Furthermore, it can mediate static adhesion of LIL from PSC, PBC, or alcoholic liver disease (ALD) to immobilized MAdCAM-1 via α4β7 and to VCAM-1 via α4β1 [78]. Both of these adhesion molecules are expressed in the portal endothelium in PBC

and PSC liver, whereas bile ducts never express MAdCAM-1 and are only occasionally positive for VCAM-1 in PBC patients [34, 35, 64, 65].

CCL28 is not detected in normal liver, but intense staining is seen in livers of patients with PSC, PBC, or ALD, not only on injured bile ducts but also on portal endothelium and on reactive bile ductules [78]. Primary human cholangiocytes can be induced to express CCL28 mRNA and protein by incubation with IL-1β or LPS. The CCL28 receptor, CCR10, is expressed on almost 17% of liver-infiltrating CD3+ T cells in inflamed liver but only 6% in healthy control liver, with the vast majority of CCR10+ cells being CD4+ T cells. Since MAdCAM-1 is not, and VCAM-1 only occasionally, detected on bile ducts, the main function of CCL28 expression in bile ducts may not be in the extravasation of lymphocytes but in their localization to bile ducts. Since binding to fibronectin is also mediated by α4β1 integrin, CCL28 may also play a role in the attachment of lymphocytes to this matrix molecule and thereby enhance their tissue retention.

Of note, Foxp3 mRNA is preferentially contained in the CCR10+ T cell population, indicating that this T cell subset includes natural regulatory T cells. A decreased frequency of Tregs has been reported from the liver and peripheral blood of PBC patients [79, 80], although increased numbers were found by others [81]. It is possible that this decrease is due to reduced expression of CCR10 or other chemokine receptors that have been implicated in the recruitment of Tregs, such as CCR8 [82] or CCR5 [83]. However, first-degree relatives of PBC patients also have a decreased frequency of Tregs in peripheral blood [79], suggesting that there is a genetic defect in the production of this lymphocyte subset rather than a defect in their homing to the liver.

CXCL12 CXCL12, also called stromal (cell)-derived factor 1 (SDF-1), is a chemokine that induces its effects via interaction with its specific receptor CXCR4. These effects include enhancing both the initial tethering of lymphocytes and their subsequent firm α4β1 integrin-mediated adhesion to VCAM-1 on endothelial cells under fluid flow [68, 84]. In addition, CXCL12 is capable of triggering α4β7-mediated binding of PBL or CD4+ T cells to MAdCAM-1 and fibronectin under shear stress [68, 73]. Furthermore, SDF-1 stimulates the chemotaxis of T cells, NKT cells, and NK cells isolated from the liver of HCV patients and healthy controls [85] and the transendothelial migration of naïve and memory CD4+ and CD8+ T cells [86]. In normal liver, SDF-1 is expressed exclusively on bile ducts in portal tracts [87, 88]. Immunoreactivity largely remains confined to the bile duct but is greatly enhanced not only in PBC and PSC liver [69, 88] but also in the liver of patients with AIH, CHC, or acute or chronic liver allograft rejection [85, 87, 88]. Interlobular and septal bile ducts show the strongest immunoreactivity, but reactive bile ductules are also positive. Both normal and diseased liver contained SDF-1 mRNA, and transcript for this chemokine was detected in laser-captured BEC, but not hepatocytes, from patients and controls [88]. Although the frequency of CXCR4 positivity was equally high in PBL and LIL, the latter exhibited greater intensity of CXCR4 expression, with both CD3+ T cells and CD19+ B cells showing higher expression levels surrounding SDF-1 positive bile ducts [87, 88]. Hepatic gene expression profiles using cDNA array analysis of PBC and PSC liver specimens reveals that CXCR4 is among the most strongly upregulated genes in PBC liver compared to normal liver and even compared to PSC liver [89]. Conversely, expression of the SDF-1 gene is more markedly enhanced in PSC than in PBC. The exclusive expression of SDF-1 on bile ducts in human liver indicates that this chemokine does not have a role in the recruitment of CXCR4+ lymphocytes to liver. However, once lymphocytes have entered the portal tract; SDF-1 functions in attracting them to bile ducts. In addition, SDF-1 may have a role in lymphocyte retention via its ability to augment their adhesion to fibronectin [73, 85, 90]. The biliary basement membrane demonstrates immunoreactive fibronectin in 80% of PBC patients but not in disease and normal control livers [91]. It remains to be determined whether this includes overexpression of the CS1 splice variant of fibronectin, which contains the binding site for VLA-4 (α4β1 integrin). Overexpression of CS1-fibronectin has been implicated in the retention of activated T cells in the synovium of rheumatoid arthritis patients [92]. Note that the interaction between lymphocytes and CS1-fibronectin is usually mediated by α4β1 integrin, but α4β7 integrin may also bind to this ligand [73]. Since SDF-1 can activate both of these integrins, it would be capable of triggering adhesion to fibronectin regardless of the integrin mediating this interaction.

Other chemokines

CXCR3 ligands

As their common names indicate, the CXC chemokines human monokine induced by IFN-γ (MIG, CXCL9), IFNγ-inducible protein of 10 kDa (IP-10, CXCL10), and IFN-inducible T cell α chemoattractant (I-TAC, CXCL11) are induced by IFNγ. They trigger adhesion and transendothelial migration under fluid flow as well as chemotaxis by signaling through a common receptor, CXCR3 [55, 86, 93]. This receptor is expressed selectively on activated effector or memory T cells [94], although more recent data suggest that activation is not an absolute requirement [93].

These chemokines are either not demonstrable in normal liver [55, 87, 95-97] or, when detected, are confined to sinusoidal endothelium and occasional portal venules [87, 98-100]. Their upregulation in various inflammatory liver diseases seems to follow chemokine- and disease-specific patterns. In PBC liver samples, IP-10 and MIG were induced in portal areas, including the damaged bile ducts [96]. In chronic liver allograft rejection, which is also characterized by progressive bile duct loss, IP-10 was induced on bile ducts in portal tracts and was upregulated on sinusoids [87]. MIG was not seen on any bile ducts but was increased on sinusoidal endothelium; I-TAC was induced on portal endothelium and some bile ducts but was not detected on sinusoids. This contrasts with the findings in CHC liver, where IP-10 and I-TAC are either found to be upregulated almost exclusively on hepatocytes [97, 99, 101] or exclusively on sinusoids [98, 102], whereas MIG has been reported to be induced or enhanced selectively on sinusoids [97, 98, 100]. A high frequency of CXCR3 lymphocytes, predominantly CD4+ T cells, was detected in PBC portal tracts, including damaged bile ducts [96]. In addition, PBC patients exhibit a significantly higher frequency of peripheral CXCR3+ CD4+ T cells compared to healthy controls. Similar results have been reported from patients with liver allograft rejection [87] and CHC patients [55, 100, 101]. Note that increased CXCR3 expression on infiltrating T cells is not confined to inflammatory diseases of the liver but seems to be a general feature of inflammation [103].

Together, these results suggest that expression of IP-10 in bile ducts may be characteristic of liver diseases where bile ducts are specifically targeted, including PBC and chronic liver allograft rejection; expression on hepatocytes seems to be typical of certain stages of forms of CHC; whereas induction or upregulation on sinusoidal cells is seen in both chronic rejection and CHC, but not in PBC. MIG also seems to participate in the recruitment of T cells to the portal tract in PBC, whereas it is expressed only on sinusoidal endothelium in chronic rejection and chronic hepatitis C. The available data on I-TAC are limited but suggest that this chemokine may be involved in the portal inflammation seen in chronic rejection but may play a role in the recruitment into the liver parenchyma via the sinusoids in CHC.

Plasma levels of IP-10 and MIG were elevated not only in PBC patients [96, 104] but also in their first degree relatives compared to controls [96]. In PBC patients, levels increased with advancing disease stage. Increased serum concentrations of IP-10 are also seen in patients with AIH [104], CHC [102, 105], and chronic hepatitis B [104], although the latter is not a consistent finding [102].

Interestingly, in situ hybridization studies indicate that IP-10 mRNA is expressed in hepatocytes of AIH, PBC, and chronic hepatitis B and C patients but not in portal areas, including the damaged bile ducts of PBC patients [104]. Similarly, others detected IP-10 transcripts mainly in hepatocytes, particularly around areas of focal and piecemeal necrosis in CHC patients [105]. On the other hand, not only a human hepatocyte-derived cell line (Huh-7) [99] but also cultured hepatic BEC [55, 106] and cultured hepatic sinusoidal endothelial cells [55, 98] are capable of producing all three CXCR3 ligands. IFNγ alone is generally sufficient to induce the production of these chemokines, whereas TNFα and IL-1β alone are often ineffective but further augment IFNγ-induced secretion. Relatively high levels of TNFα and IFNγ are present in most inflammatory liver diseases, including PBC, CHC, and liver allograft rejection. Therefore, other microenvironmental factors must contribute to the disease-specific expression patterns of the CXCR3 ligands. These could include HCV infection itself since it has been shown that transfection of HCV proteins or HCV RNA can stimulate the transcription and protein synthesis of chemokines, including IP-10 MIG and I-TAC [99, 107]. In PBC, LIL may play a role in further enhancing the chemokine production of BEC induced by certain other stimuli [106]. In addition, PBC LIL has been reported to exhibit enhanced chemotaxis to IP-10 and other chemokines compared to LIL from patients with viral hepatitis.

CXCL16 Another chemokine that might be involved in the recruitment of lymphocytes to bile ducts is CXCL16, constitutively expressed on bile ducts, hepatocytes, sinusoids, and to a lesser extent, on portal vessels [108]. Expression of this chemokine is upregulated on bile ducts in liver tissue from PBC and PSC, but not CHC, patients, whereas hepatocyte and sinusoid staining is enhanced in CHC. This pattern recaptures the disease-specific distribution of CXCR3 ligands. In matched samples, significantly higher percentages of LIL than PBL were positive for the CXCL16 receptor, CXCR6, in liver donors as wells as patients with end-stage CHC [108]. In cell culture, cholangiocytes demonstrate stronger expression of CXCL16 than hepatocytes and sinusoidal endothelial cells, which were nonetheless also positive. This chemokine was shown to enhance the adhesion of LIL and, to a lesser degree, PBL to primary cholangiocytes under static conditions, by activating α4β1 integrin (VLA-4) and thereby increasing its ability to bind to VCAM-1. This suggests that CXCL16 is important for the retention of lymphocytes on bile duct epithelium either through VCAM-1 or, since VCAM-1 is rarely detectable even in PBC and PSC, possibly through the other α4β1 integrin ligand, fibronectin. There are indications, though, that CXCR6 may play a more general role in the targeting of lymphocytes to, or their localization within, inflamed tissue

since increased numbers of CXCR6 T cells are not only found in inflamed liver but also in inflamed synovium of psoriatic and rheumatoid arthritis [109]. Interestingly, CXCR6 is preferentially expressed on type 1 (IFNγ-expressing) CD4+ and CD8+ T cells, particularly by highly differentiated effector Th1 cells and CD56+ granzyme A-expressing effector CD8+ cells. These are the cell types that are implicated in the destruction of bile ducts in PBC.

Fractalkine Fractalkine (CX3CL1) is an unusual molecule in that it (1) is the first and, to date, only member of the CX3C subclass of chemokines, (2) exists in both membrane-bound and soluble form, and (3) is both an adhesion molecule and a chemokine. It consists of a chemokine domain atop a mucin-like stalk connected to a single transmembrane region and a short intracellular tail. Fractalkine in its membrane-anchored state mediates leukocyte adhesion in an integrin-independent manner under static and flow conditions [110, 111]. There are indications that as in the interactions between other adhesion molecules and their lymphocyte ligands, adhesion to fractalkine requires a chemokine-mediated activation step [30]. In contrast, soluble fractalkine acts as a true chemokine capable of activating integrin ligands of other adhesion molecules and fibronectin [112, 113] and of triggering chemotaxis and transendothelial migration of certain monocyte and lymphocyte subsets [114, 115].

Both adhesion and chemotaxis are mediated by interactions between the chemokine domain of fractalkine with the fractalkine receptor CX3CR1 [115], but only chemotaxis requires signaling through G proteins. The two forms of fractalkine can show antagonistic activities [115-117]. CX3CR1 is expressed on monocytes, particularly CD16+ monocytes [118], but, above all, is a defining feature of cytotoxic effector lymphocytes, as identified by their cell-surface expression of CD57 and CD11b and intracellular expression of granzyme B and perforin [117]. Included in this group are terminally differentiated CD8+ T cells, NK cells, γδ T cells, and a small subgroup of CD4+ T cells. Of note, among CD4+ T cells, expression of CX3CR1 is almost exclusively found on those lacking the costimulatory molecule CD28 [116, 119]; all $CD28^-$ CD4+ T cells are positive for CX3CR1 [119]. In addition, CX3CR1 expression and responsiveness to fractalkine is seen predominantly in Th1 cells [120]. However, since CX3CR1 expression is confined to a small subset of CD4+ T cells, the relevance of these findings remains to be established.

Immunohistochemistry revealed that CX3CL1 is expressed on endothelial cells of small vessels in normal liver and faint staining is also detected on some bile ducts [121]. In liver biopsy samples from PBC patients, both the signal intensity and the number of bile ducts showing immunoreactivity is clearly increased, whereas neither the pattern nor the intensity of staining is altered in PSC, extrahepatic biliary obstruction, or CHC. From these data, it would appear that upregulation of fractalkine on bile ducts is specific to PBC. However, another group showed fractalkine expression in inflammatory foci surrounding regenerating nodules and also in bile-duct-like structures in CHC [122]. Even stronger immunoreactivity was detected in acute hepatitis due to acute HBV infection. In addition to areas of inflammation and necrosis, there was intense staining in regenerating epithelial cells within ductular reactions.

The fractalkine receptor, CX3CR1, was expressed in a few mononuclear cells in the portal tracts of normal livers and expression was somewhat increased in other liver diseases but was significantly higher in PBC patients, where CX3CR1-positive lymphocytes were found predominantly around damaged bile ducts [121]. Of note, CX3CR1 expression is rapidly downregulated on CD4+ T cells after receptor engagement by fractalkine [119]. Consequently, CX3CR1+ CD4+ T cells could not be detected in inflamed colonic tissue from IBD patients, whereas $CD28^-$CD4+ T cells, which all express this receptor, could be demonstrated in inflamed mucosa. Therefore, $CD28^-$ CD4+ T cells may have escaped detection in PBC liver [121]. Note, however, that the proportion of $CD28^-$ CD4+ T lymphocytes is significantly increased among PBL and intrahepatic T lymphocytes of PBC patients compared to healthy controls [123]. In particular, the intra-epithelial lymphocytes of small bile ducts in PBC patients contained a much higher number of $CD28^-$ CD4+ T cells than seen in other liver diseases or normal liver [124]. In contrast to CD28+ CD4+ T cells, $CD28^-$ CD4+ T cells are cytotoxic, express high levels of IFNγ, and are resistant to apoptosis. They are strongly implicated in autoimmunity since their frequency is significantly increased in a variety of autoimmune diseases. The detection of fractalkine on BEC in PBC together with the observation that this chemokine can act as a chemoattractant for the $CD28^-$ subset of CD4+ T cells [117, 119] suggest an important role for fractalkine in the recruitment of these cells to the bile ducts. In addition, it has been shown that fractalkine can also function as a co-stimulatory molecule and thereby increase granule exocytosis and IFNγ production in $CD28^-$ CD4+ T cells [116].

PBC patients exhibit a much higher precursor frequency of CD4+ T cells that do not require co-stimulation for proliferation and IFNγ production in response to the major PBC antigen PDC-E2 163-176 [123]. Furthermore, some of the co-stimulation-independent clones established from these PDC-E2 163-176-specific CD4+ T cells lacked CD28 expression. Nonetheless, this co-stimulatory function of fractalkine may not play an important role in PBC, since BECs, which are the major cell type expressing CX3CL1 in PBC liver, have been shown not to act as antigen-

presenting cells but to inhibit antigen-specific activation of T cells regardless of their co-stimulation requirement [125].

The detection of CX3CR1+ T cells in the liver of patients with PBC and viral liver diseases suggests that unlike $CD28^-$ CD4+ T cells, other T lymphocyte subsets do not decrease their CX3CR1 expression after receptor engagement. The group of cytotoxic effector lymphocytes defined by expression of the fractalkine receptor CX3CR1 includes γδ T cells, 70% of which display this receptor on their cell surface [117]. γδ T lymphocytes have been implicated in various autoimmune diseases, and their frequency is increased in peripheral blood and liver of patients with PBC and PSC [126, 127]. It seems likely, however, that CD8+ T cells, which are strongly implicated in the bile duct damage seen in PBC and which also frequently express CX3CR1, represent the major CX3CR1 + population in PBC liver. The co-expression of fractalkine and CX3CR1 on BEC, as seen in PBC [121], CHC, and acute hepatitis due to HBV infection [122], suggests that interactions between fractalkine and its receptor may also be involved in tissue generation, particularly the recruitment of epithelial cells and their arrangement into ductular structures.

Macrophage inflammatory proteins and monocyte chemoattractant proteins Although originally named for their ability to attract monocytes or macrophages, certain members of the macrophage inflammatory protein (MIP) and monocyte chemoattractant protein (MCP) families can also induce chemotaxis and transendothelial migration of T cells, in particular activated or memory CD4+ and CD8+ T lymphocytes [86, 128]. In normal liver, portal vessels constitutively express MIP-1α, MIP-1β, and MCP-1, sinusoids and bile ducts show no or only weak immunoreactivity, and hepatocytes are always negative [57, 98, 129, 130]. There is little information on the role of these chemokines in PBC and PSC. MCP-1 is not upregulated on BEC in PBC. However, mononuclear leukocytes in the portal tracts express MCP-1, MCP-2, and MCP-3, and this may in turn recruit additional T cells into this area. Mainly, however, MCP-2 and MCP-3 appear to be involved in the recruitment of macrophages and the formation of granulomata.

Concluding remarks

The existing data on T lymphocyte recruitment to PSC and PBC liver suggest the following scenario: inflammatory signals in both PBC and PSC liver induce or enhance the expression of adhesion molecules such as ICAM-1, VCAM-1, and MAdCAM-1, whereas VAP-1 expression is not altered. At the same time, a variety of chemokines are also upregulated. In PSC, expression of CCL25, CCL21, and CCL28 all are implicated in activating α4β7 integrins and thereby enhancing lymphocyte binding to MAdCAM-1. In addition, CCL21and CCL28 could promote adhesion to VCAM-1 by activating α4β1 integrin. The same holds true in PBC, except that CCL25 does not participate. Several of these chemokines have also been shown to enhance transendothelial migration. Data on other chemokines are largely confined to PBC. They indicate that induced or upregulated expression of MIG and IP-10 in portal tracts may also contribute to enhanced lymphocyte recruitment into PBC liver. Once lymphocytes have entered the portal tract tissue, they are recruited to, and retained around, the bile ducts by the combinatorial or sequential action of CXCL12 (SDF-1), CXCL16, fractalkine (CX3CL1), CCL28, and possibly MIG and IP-10. At this point, the relative importance of each of these chemokines in the recruitment or the retention of lymphocytes around the bile ducts remains unclear. These limited data underscore the complexity of lymphocyte recruitment and homing to the liver. The data also suggest that there is no liver addressin, but instead, liver homing is likely to require complex combinations of adhesion molecule ligands and chemokine receptors that provide not only entry into the liver but also localization to specific liver compartments.

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