Review

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Return to sender: Lymphocyte trafficking mechanisms as contributors to primary sclerosing cholangitis

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Summary

Primary sclerosing cholangitis (PSC) is an inflammatory disease of the biliary tree, characterised by stricturing bile duct disease and progression to liver fibrosis. The pathophysiology of PSC is still unknown. The concurrence with inflammatory bowel disease (IBD) in about 70% of cases has led to the hypothesis that gut-homing lymphocytes aberrantly traffic to the liver, contributing to disease pathogenesis in patients with both PSC and IBD (PSC-IBD). The discovery of mutual trafficking pathways of lymphocytes to target tissues, and expression of gut-specific adhesion molecules and chemokines in the liver has pointed in this direction. There is now increasing interest in using drugs that intervene with these trafficking pathways (*e.g.* vedolizumab, etrolizumab) for the treatment of PSC-IBD. In this review we discuss what is currently known about the immunological interactions between the gut and the liver in concomitant PSC and IBD, as well as potential therapeutic options for intervening in these mechanisms.
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Introduction

Primary sclerosing cholangitis (PSC) is a rare, chronic liver disease, characterized by inflammation of the intra- and extrahepatic bile ducts, leading to destruction of the biliary epithelium and end-stage liver disease. There is an urgent clinical unmet need for treatment options for PSC as there is still no medical therapy with a proven effect on disease progression.[1]

PSC is strongly associated with inflammatory bowel disease (IBD), giving rise to some intriguing and still unexplained questions regarding these disease entities. Approximately 70% of patients with PSC have or will develop concurrent IBD, of which the majority, about 80%, will suffer from ulcerative colitis (UC).[2–4] Conversely, the presence of PSC among the total population of patients with IBD is rare, with a prevalence varying between 1.7–3.8%.[5,6] It has been proposed that IBD in PSC represents a distinct phenotype, characterised by a higher frequency of pancolitis with involvement of the right colon and a relatively mild disease course, and a higher occurrence of pouchitis after colectomy, compared to IBD without PSC.[7–11] This assumption is strengthened by genome-wide association studies showing a higher genetic correlation between UC and Crohn's disease (CD) than between either of them and PSC-IBD.[12,13]

Various clinical observations have led to the assumption that there is an interaction between the gut and the liver in patients with PSC. As for concomitant IBD, in the majority of cases clinical symptoms of IBD precede the diagnosis of PSC. However, IBD can also develop after PSC diagnosis or even years after liver transplantation.[2,14,15] It is possible that microscopic abnormalities of IBD are already present at diagnosis of PSC, but do not result in clinical symptoms. Supporting this, Jorgensen *et al.* showed in a cohort of 184 patients with PSC that 89% had histopathological abnormalities compatible with IBD, whereas only 47.5% had endoscopic signs of inflammation.[16] In terms of disease activity, the correlation between IBD and the disease course of PSC is less clear. Patients with severe colitis tend to have less severe PSC in terms of need for liver transplantation, although a protective effect of IBD medication on progression to end-stage liver disease cannot be ruled out.[17] Furthermore, it has been reported that colectomy prior to the diagnosis of PSC confers a decreased risk of liver transplantation or death.[18] Similarly, patients with PSC-UC and a more progressive form of PSC requiring liver transplantation seem to have a milder form of UC, less frequently requiring colectomy.[19,20]

Several hypotheses regarding the pathogenesis of PSC have been proposed, such as the toxic bile acid hypothesis and the hypothesis that translocation of microbiota from the gut to the liver triggers an aberrant cholangiocytic response.[21,22] The prominent association between PSC and IBD has fuelled another hypothesis, which states that long-lived memory T lymphocytes expressing gut-homing markers, migrate into the liver via aberrantly expressed mucosal adhesion molecules and chemokines in the liver.[23] The aim of this review is to present an overview of the current knowledge regarding lymphocyte recruitment and homing in the human liver and intestine in PSC-IBD.

Lymphocyte homing to the gut and liver

Recruitment of lymphocytes

In 1990, Butcher and Springer described the lymphocyte homing paradigm.[24,25] After leaving the primary lymphoid organs, naïve lymphocytes

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Key point

PSC is strongly associated with IBD, giving rise to the hypothesis that mature gut-homing lymphocytes aberrantly traffic to the liver to induce inflammation.

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circulate through secondary lymphoid tissues such as peripheral lymph nodes, spleen and gut-associated lymphoid tissues (GALTs). To trigger an immune response, these naïve T and B lymphocytes are primed in the secondary lymphoid tissues via interaction with antigen-presenting cells, dendritic cells (DCs) and follicular dendritic cells, respectively.[26] Subsequent expression of tissue-specific homing molecules, enables them to migrate back to their target tissues as mature effector T lymphocytes that can proliferate locally. Recruitment of lymphocytes from the blood into lymph nodes takes place via high endothelial venules. In order to be recruited from the circulation into tissue, a multistep process of lymphocyte-endothelial recognition has to take place.[27] Fast flowing lymphocytes have to undergo a process of tethering, rolling and adhesion to the endothelium. For the initial step of tethering and rolling, interactions between selectins on the lymphocyte and glycosylated ligands on the endothelium are required.[25] Together with chemokines, this will trigger lymphocyte activation and firm attachment to the endothelium via interactions between integrins and adhesion molecules such as vascular cell-adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) on endothelial cells.[26] Chemoattractants can then mediate the transmigration of the cells through the endothelium into the specific microenvironments.

Recruitment of lymphocytes to the gut

In the gut, a system of tissue-specific lymphocyte trafficking plays a key role in protecting the intestine from invading pathogens. The general concept in the field is that naïve lymphocytes recirculate through organised lymphoid tissue (*e.g.* Peyer's patches and mesenteric lymph nodes), where they become activated. These activated effector cells will then seed the lamina propria. One of the key players in this lymphocyte trafficking mechanism is mucosal vascular addressin cell-adhesion molecule 1 (MAdCAM-1). MAdCAM-1 is an adhesion molecule, widely expressed in high endothelial venules of the gut-associated lymphoid tissue.[28]

Pathogens penetrating the mucosal barrier are recognised by dendritic cells or microfold cells in the epithelial layer. High endothelial venules in gut-associated lymphoid tissue express CC-chemokine ligand 21 (CCL21), thereby attracting circulating naïve lymphocytes expressing its receptor, CC-chemokine receptor 7 (CCR7), as well as L-selectin (Fig. 1.1).[29,30] Some DCs from the gut can produce retinal dehydrogenase-2, the rate-limiting enzyme for the conversion of retinal to retinoic acid (vitamin A metabolite). Retinoic acid is required to activate nuclear receptors that induce transcription of the genes that encode the gut-homing receptors integrin α4β7 and CCR9 on T lymphocytes.[31] As a result, interaction between the antigen-expressing DCs and naïve lymphocytes results in a reduction in the expression of CCR7 and L-selectin, and upregulation of expression of integrin α4β7 and CCR9 (Fig. 1.2). These so-called gut-primed effector T cells (Teff) can enter the lamina propria through the interaction of integrin α4β7 with MAdCAM-1, which is expressed on endothelial cells (Fig. 1.3, Table 1).

In IBD, the concept of uncontrolled recruitment of lymphocytes is generally accepted and multiple drugs intervening in this trafficking pathway are currently being used. Although MAdCAM-1 is constitutively expressed in the small intestine and colon of patients with IBD, as well as healthy controls, during active inflammation, MAdCAM-1 expression is increased.[28,32] Also VCAM-1, the endothelial ligand for both α4β1 and α4β7 (Table 1), is upregulated in IBD, supporting lymphocyte recruitment both to the small bowel and colon.[33] The response triggered by interfering with α4β7-dependent homing is not yet fully clarified. In a humanised mouse model of CD, inhibition of α4β7-dependent homing of Teff cells was bypassed by homing to the ileum through integrin α4β1.[34] In a recent study, a role for innate immunity was proposed, consisting of a switch to wound-healing macrophages after inhibition of α4β7.[35]

As there are substantial anatomical and physiological distinctions between the small and large intestine, their immune compartments also contain differences. The small intestine contains a larger proportion of intra-epithelial lymphocytes compared to the colon, whereas proportions of Th1 and Th2 cells do not differ between the colon and ileum.[36] Furthermore, T cells with a regulatory phenotype (Tregs) seem to be more abundant in colonic tissue, at least in mice.[37] Since the majority of patients with PSC suffer from concomitant colonic disease, it may be of particular interest whether colonic homing requires different homing markers and mechanisms compared to the small intestine. In the small intestine, CCL25 and CCR9 seem to be key regulators. In non-inflammatory conditions, CCL25, the chemokine binding to CCR9 on intestinal lymphocytes, is expressed in the epithelium of the small intestine, especially in the crypts and lower villus epithelium.[38,39] Additionally, expression on endothelial cells in the lamina propria was described in humans, albeit only by 1 group.[40] It has been postulated that CCL25, could diffuse to and be presented by the vascular endothelium, in order to facilitate transendothelial migration of $\alpha4\beta7^{+}$ $CCR9^{+}$ lymphocytes.[38] Although it was long thought that CCL25 expression was restricted to the small bowel, Trivedi *et al.* recently identified the presence of CCL25 in colonic tissue in inflammatory conditions.[39] They also observed significantly more T cells expressing its receptor CCR9 in the colonic tissue of patients with UC refractory to medical therapy compared to healthy controls.

In contrast to the small intestine, in colonic tissue, recruitment of T cells predominantly takes

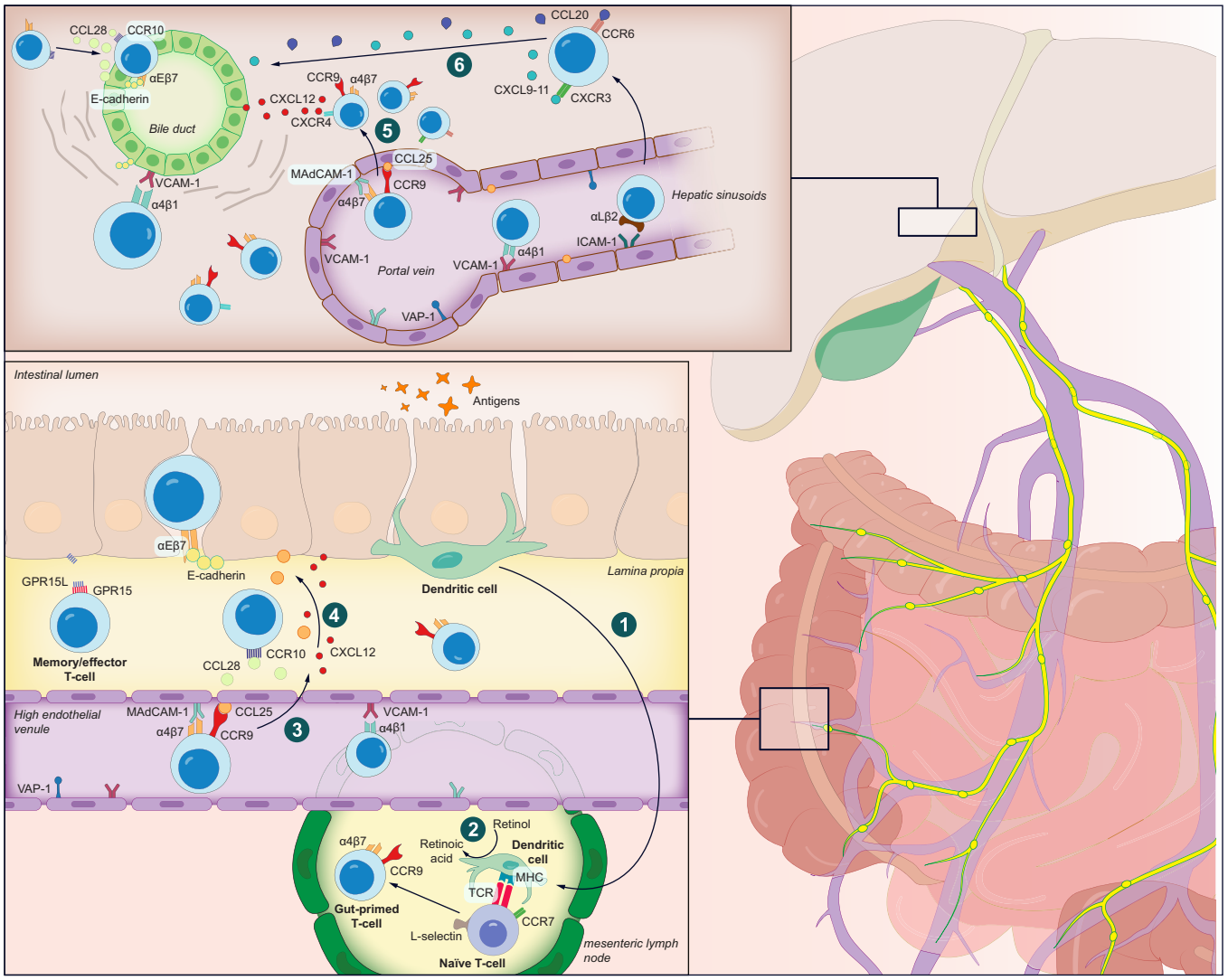

Fig. 1. Overview of aberrant homing in the gut and liver in primary sclerosing cholangitis. Naïve lymphocytes expressing CC-chemokine receptor 7 (CCR7) as well as L-selectin enter the gut-associated lymphoid tissue. Dendritic cells (DCs) which recognised pathogens penetrating the mucosal barrier, will migrate to the draining lymphoid structures to present their antigen to these naïve T cells (1). Via their production of retinal dehydrogenase to transform retinol into retinoic acid, the naïve T cells are imprinted with the gut-homing receptors integrin α4β7 and CC- chemokine receptor 9 (CCR9) (2). These so-called gut-primed T cells will re-circulate into the lamina propria via venules by binding to MAdCAM-1 on endothelium of the blood vessels as well as via interaction between CCR9 and CCL25 (3). Several chemoattractants (e.g. CCL25, CXCL12) can direct the lymphocytes into the lamina propria (4). In primary sclerosing cholangitis, it is hypothesised that gut-primed memory T cells expressing α4β7 and CCR9 could migrate to the liver via aberrantly expressed MAdCAM-1 and CCL25 by portal endothelial cells (5). Expression of CCL28 by biliary epithelial cells could provide a signal to attract CCR10 positive T cells to the portal tracts. Additionally, chemokines including CXCL12 could play a role in retaining CCR9+ lymphocytes around bile ducts. IL-17 stimulates CCL20 and CXCL9-11 expression by biliary epithelium, leading to recruitment of CCR6+ CXCR3+ Th17 cells to the bile ducts (6).

Table 1. Receptor-ligand pairs.

Adhesion molecule	Ligand
MAdCAM-1	α4β7, α4β1, L-selectin
VAP-1 (AOC3)	Siglec-9, Siglec-10
E-cadherin	αEβ7, α2β1
ICAM-1	αLβ2
VCAM-1	α4β1, α4β7
Chemokine receptor	**Ligand**
CCR6	CCL20 (MIP-3α)
CCR7	CCL19, CCL21
CCR9	CCL25 (TECK)
CCR10	CCL27, CCL28
CXCR4	CXCL12 (SDF-1)

Receptor-ligand pairs and alternative names. AOC3, amine oxidase copper containing 3; MIP-3α, macrophage inflammatory protein-3; TECK, thymus-expressed chemokine.

place via CCR10 and G-protein coupled receptor 15 (GPR15) (Fig. 1.4).[41–43] CCR10 is a chemokine receptor expressed by both T and B cells. Mucosal homing of CCR10^{+} lymphocytes in the colon is driven by binding to CCL28, a chemokine expressed by the epithelium, whose expression is upregulated during inflammation.[44] The orphan chemoattractant receptor GPR15 has recently been described as a homing receptor of Tregs to the colon, particularly in mice.[41,42] However, in humans, GPR15 was found to be abundantly expressed on Th2 cells in the normal and inflamed colon, rather than on Tregs.[41] The recently described ligand for GPR15, GPR15L was found to be expressed by epithelia that are in close contact

with a microbial environment, including the colon, skin and cervix.[45] Expression of GPR15L is only minimally influenced by inflammation in the context of UC, whereas no expression is seen in the liver.[45,46] It is thought that the GPR15/GPR15L interaction is involved in sustaining the inflammatory environment in UC, however a role for GPR15 in lymphocyte homing in patients with PSC-IBD has not been established yet.

Recruitment of lymphocytes to the liver

Like the skin and gut, the liver is an important site of antigen exposure with its own response to invading pathogens. Several lymphocyte subsets including T cells, B cells, natural killer (NK) and natural killer T (NKT) cells commonly reside in the liver under homeostatic conditions. Whereas gut-activated T cells are primed in lymphoid structures (*e.g.* GALT), liver-activated T cells are primed in the liver itself. The adhesion of lymphocytes into the liver differs from the classical migration pathway as described earlier; firstly, extravasation of lymphocytes occurs mainly in the hepatic sinusoids instead of in the venules seen in most other tissues. Secondly, in the hepatic sinusoids this process is not dependent on selectins, at least not in mice, and often occurs independently of a rolling step.[47–49] However, there is an important role for lymphocyte adhesion molecules expressed by hepatic sinusoidal endothelial cells, including vascular adhesion protein 1 (VAP-1), ICAM-1 and the common lymphatic endothelial and vascular endothelial receptor-1 (CLEVER-1), also known as stabilin-1, which are constitutively expressed in the liver, but increased upon inflammation.[48,50] $CD8^+$ T cells have been shown to adhere to the sinusoidal endothelium via interactions between either VCAM-1 and integrin $\alpha4$, or ICAM-1 and integrin $\alpha L\beta2$; adhesion can also take place independently of these molecules (Fig. 1.6).[49,51] Involvement of secreted chemokines including CXC-chemokine ligand (CXCL)9, CXCL10 and CXCL11 attracts both regulatory and effector T cells, which express chemokine receptor CXCR3, to enter the liver via the sinusoidal endothelium (Fig. 1.6).[52,53] The biliary epithelium also plays a role in lymphocyte recruitment in response to inflammatory signals, whereupon cholangiocytes express VCAM-1 to support T-cell binding via $\alpha4\beta1$.[54]

Key point

Lymphocyte homing to the intestine seems to be rather similar in patients with IBD and concomitant PSC, as for IBD in general.

Evidence for a role for 'gut-homing' cells in PSC-IBD

Gut-liver axis in PSC-IBD

PSC is characterised by peribiliary infiltrates, mainly consisting of T lymphocytes. Interestingly, this infiltrate contains a subset of T lymphocytes expressing integrin $\alpha4\beta7$, suggesting a gut origin whereas in normal liver, this is only occasionally the case.[55] This aberrant gut-homing lymphocyte hypothesis was further elaborated on by Adams *et al.* who proposed that long-lived mucosal T lymphocytes are recruited to the liver via aberrantly expressed mucosal adhesion molecules and chemokines in the liver that are normally restricted to the gut.[56] This gut origin is further supported by the finding that neither liver dendritic cells nor hepatic stellate cells (HSCs) are able to imprint gut trophism on $CD8^+$ T cells.[57] Additionally, in a murine model, $CD8^+$ T cells activated in GALT caused immune-mediated cholangitis in an antigen-dependent manner, and gut-primed $CD8^+$ T cells activated in GALT could migrate to the liver, whereas liver-activated $CD8^+$ T cells did not home to the intestine.[58,59] Conversely, one *in vitro* study showed that murine sinusoidal endothelium could induce gut trophism on $CD4^+$ T cells.[60]

In general, there are no differences in the amount of total circulating $CD4^+$ and $CD8^+$ T cells in the peripheral blood of patients with PSC-UC and UC compared to healthy controls.[61,62] However, patients with PSC-UC have increased frequencies of colonic Th1 cells as well as larger proportions of CXCR3-expressing $CD8^+$ T cells in the colon and peripheral blood compared to patients with UC.[61,63] Also, a role for innate lymphoid cells (ILCs) has been proposed, in that increased numbers of lineage$^-$ $CD127^+$ ILCs were found in the colons of patients with PSC-UC compared to those with UC, giving rise to the idea that PSC-UC represents a distinct immunological phenotype compared to UC.[61]

Contribution of various subsets of T cells in PSC liver pathology

In PSC liver, increased numbers of intrahepatic $CD4^+$ T cells negative for CD28, a costimulatory molecule required for T-cell activation and survival, localise close to the bile ducts.[64] This increased frequency of $CD28^-$ T cells was not seen in the peripheral blood of patients with PSC compared to healthy controls.[62,64] Downregulation of CD28 expression can be triggered by a tumor necrosis factor (TNF)-α rich environment, which could explain the locally increased numbers in PSC livers.[64,65] Liver infiltrating $CD4^+CD28^-$ T cells express high levels of different chemokine receptors that play a role in tissue infiltration and localisation close to bile ducts, including CX3CR1, CCR10 and CCR9, compared to peripheral circulating cells.[64] Upon activation, $CD28^-$ effector memory T cells can release high levels of the pro-inflammatory cytokines TNF-α and interferon-γ (IFN-γ), which further promotes inflammation, and triggers biliary epithelial cells to express adhesion and costimulatory molecules including ICAM-1, HLA-DR and CD40.[64] The potential relevance of the cell surface molecule CD28 in PSC was strengthened by the identification of the CD28 locus as a risk factor in PSC development.[66]

Th17 cells

Biliary epithelial cells can express the IL-17 receptor IL-17RA, and can therefore react on locally

secreted IL-17 by Th17 cells.[67] The cytokine IL-17A has profibrotic properties, leading to hypersensitivity of HSCs to transforming growth factor (TGF)-β.[68] In the acute phase, this could be beneficial for liver wound healing, but in cases of chronic liver disease like PSC, this could cause enhanced fibrogenesis. The contribution of IL-17 to PSC has been described in different studies. IL-17 stimulates CCL20 and CXCL9-11 expression by the biliary epithelium, leading to recruitment of $CCR6^+$ $CXCR3^+$ Th17 cells to the bile ducts (Fig. 1.6).[67] An increased response of Th17 and Th1/Th17 cells after pathogen stimulation was found in the peripheral blood of patients with PSC, as well as an accumulation of IL-17A expressing T cells around bile ducts and areas of neoductular proliferation.[69] Furthermore, a selective enrichment of γδT cells capable of producing both IL-17 and IFNy was present in PSC livers, compared to hepatitis C virus (HCV) livers where mainly IFNy secretion was seen.[70,71] Overall, infiltrating Th17 cells seem to play a role in sustaining inflammation in PSC.

Regulatory T cells

The role Tregs play in PSC remains unclear. Tregs are thought to limit local damage resulting from infectious challenges to a host and have critical functions in maintaining tolerance against autoantigens. Genetic studies revealed single nucleotide polymorphisms within the IL-2 receptor alpha (IL-2RA) locus and the IL-2/IL-21 locus that were associated with PSC.[66,72] IL-2RA (CD25) is a type 1 transmembrane protein constitutively expressed by Tregs, whereas IL-2, the ligand for IL-2R, is required for expansion of Tregs and induction of their suppressive function.[73] Interestingly, *Il2ra*$^{-/-}$ mice spontaneously develop both intestinal and biliary inflammation, and in a T-cell mediated colitis model with low abundance of Tregs, mice developed liver inflammation and fibrotic signs.[74,75] A significantly lower number of Tregs were found in peripheral blood from patients with PSC than from patients with primary biliary cholangitis (PBC) or healthy controls. The lower number of Tregs was not associated with concomitant IBD.[76] Also, the proportion of Tregs in the liver was reported to be significantly reduced in patients with PSC, at the time of diagnosis as well as at the time of end-stage disease.[76,77] This finding suggests that impaired production or recruitment of Tregs, which reduce inflammation, may play a causal role in PSC. Conversely, another study reported a marked increase in $FoxP3^+$ cells around heavily inflamed portal tracts in chronically inflamed livers of patients with PSC, PBC and alcohol-related liver disease (ALD), suggesting that interactions between CCL28 and CCR10 on Tregs could play a role.[52]

Evidence for gut-homing molecules in PSC liver

The fact that not all patients with IBD develop liver disease suggests that there should also be a trigger in the liver, which could attract circulating lymphocytes into the liver tissue.

A recent study looking at shared clonotypes of the T-cell receptors of matched colon, liver and blood samples, showed a higher level of overlap between paired PSC-IBD samples than normal gut and liver samples, suggesting that memory T cells in the gut and liver of patients with PSC-IBD react to shared antigens.[78] Furthermore, there is also evidence that certain adhesion molecules and chemokines are aberrantly expressed in PSC livers. Thus far, transcriptomic analysis of non-end-stage PSC livers is still lacking. This may provide more insight into which trafficking molecules are involved in PSC.

MAdCAM-1 - α4β7

One of the key findings supporting the hypothesis that long-lived memory T cells primed in the gut could migrate to liver tissue in patients with PSC, is the presence of mucosal adhesion molecule MAdCAM-1 in PSC livers (Fig. 1.5). In humans, MAdCAM-1 is widely expressed during early foetal development, whereas it gradually becomes polarised to mucosal vessels and downregulated in other tissues after birth.[79] Its expression is then restricted to endothelial cells lining blood vessels of only a few distinct tissues, including the gastrointestinal (GI) tract (colon and small intestine), mucosal associated lymphoid tissues of the GI tract, and to a lesser extent pancreas, gallbladder and spleen.[28,79,80] Only a few studies have looked into MAdCAM-1 expression in liver tissue. While at least 4 studies showed that the MAdCAM-1 protein is not present in normal liver tissue, 3 studies have shown aberrant expression of MAdCAM-1 on large and small portal vein endothelium in several inflammatory liver diseases.[23,28,80,81] Under inflammatory conditions, MAdCAM-1 expression was shown on portal vein endothelium, portal tract venules and vessels of the peribiliary capillary plexus (Table 2). The presence appeared focal, in which only a proportion of portal tracts stained positive.[23,80] Moreover, MAdCAM-1 expression was also seen in association with lymphoid aggregate and follicle formation, where cells were negative for CD34, a marker of vascular endothelium.[80,81] The presence of MAdCAM-1 was more prominent in PSC and autoimmune hepatitis (AIH) livers than in PBC and HCV livers, suggesting a correlation with IBD.[23]

There is a lot of variability in the presence of MAdCAM-1 in PSC livers between different studies. In needle biopsies of non-end-stage PSC livers, Ala *et al.* failed to detect MAdCAM-1, whereas Hillan *et al.* did detect MAdCAM-1 staining in 20% of specimens.[80,81] In explanted PSC livers, these numbers were much higher, with MAdCAM-1 present in 69–100% of liver sections.[23,80,81] This discrepancy may in part be explained by the focal nature of expression, especially in small liver biopsies containing little portal tracts, leading to an

Key point

The pro-inflammatory and pro-fibrotic cytokine IL-17 also plays a role in recruitment of Th17 cells in the inflamed PSC liver.

Key point

Aberrant expression of adhesion molecule MAdCAM-1 could cause adhesion of effector memory T cells expressing integrin α4β7 into the liver.

Table 2. Adhesion molecules and their protein expression in normal and PSC liver.

Adhesion	Normal liver	PSC liver
MADCAM-1	Not expressed*	Inflamed portal vein/sinusoidal endothelium Peribiliary capillary plexus
VAP-1	Portal endothelium Sinusoidal endothelium	Increased sinusoidal expression Fibrous septa
E-CADHERIN	Biliary epithelium Hepatocytes	Loss of expression in biliary epithelial cells No changes in hepatocytes
ICAM-1	Portal endothelium Sinusoidal endothelium	Increased endothelial expression Biliary epithelial cells
VCAM-1	Portal endothelium	Increase endothelial expression Biliary epithelial cells

PSC, primary sclerosing cholangitis.
* Low levels of mRNA expression found in normal liver by Ala *et al.*[81]

Table 3. Overview of cells expressing integrin α4β7, αEβ7 or α4β1.

	Cell expression	Activating chemokine(s)
α4β7	Naïve T cells Memory T cells Regulatory T cells B cells Eosinophils Natural killer cells Monocytes	CXCL12, CCL21, CCL25, CCL28
αEβ7	Memory T cells Regulatory T cells Dendritic cells Mast cells	CCL25
α4β1	Memory T cells B cells Eosinophils Natural killer cells Monocytes Neutrophils	CXCL12

underestimation. However, in the study of Hillan *et al.*, both needle biopsies and autopsy specimens of patients with HCV showed the same percentage of cases expressing MAdCAM-1, suggesting that the observed difference between PSC and HCV could also be disease specific. Another explanation for the variability of the results may be the different detection techniques used. For example, Ala *et al.* showed in normal liver tissue there is no protein expression of MAdCAM-1, but *MAdCAM-1* mRNA is constitutively expressed, albeit only in small amounts.[81] In addition, the differences in disease stage or grade could cause variability. It has been shown that *MAdCAM-1* mRNA expression is significantly upregulated in cirrhotic livers compared to normal liver, however it is not known how this relates to different disease stages.[81] There does seem to be a positive correlation between histologic grade (degree of inflammation) and MAdCAM-1 presence in HCV needle biopsies, however this has not yet been evaluated for PSC.[80]

Whether MAdCAM-1 upregulation is a critical event in the pathogenesis of inflammatory liver diseases or whether it is more a secondary epiphenomenon is still under debate. Possibly, the foetal downregulated MAdCAM-1 cannot be suppressed in inflammatory conditions. Both in mice and in humans, expression of MAdCAM-1 can be induced by TNF-α and IL-1, which is regulated through the nuclear factor (NF)-kappa B pathway.[82–84]

Integrin α4β7 is present on approximately 50% of circulating T cells in the peripheral blood of healthy individuals.[23,85] This proportion is the same in the peripheral blood of patients with PSC, whereas about 10–30% of CD3+ liver infiltrating T cells of patients with PSC are α4β7 positive.[23] Integrin α4β7 is expressed on a wide range of leukocytes, including naïve and memory $CD4^+$ and $CD8^+$ T cells, B cells, eosinophils, NK cells, and to a lesser extent monocytes (Table 3).[85,86] The chemokines CXCL12, CCL21, CCL25 and CCL28 all promote binding of α4β7+ lymphocytes to MAdCAM-1, of which CXCL12 appears to have the most potent effect (Table 3).[33] Expression of CCL21, the ligand of CCR7, was found to be increased in portal tracts of patients with PSC, which could have the additional effect of attracting CCR7+ α4β7+ lymphocytes into the liver.[87,88]

It could be that in the situation of inflammation, local release of TNF-α could induce expression of MAdCAM-1, which together with stimulatory chemokines could promote the influx of integrin-expressing leukocytes.

CCL25 - CCR9

In explanted PSC livers, CCL25 was found to be expressed on hepatic sinusoidal endothelium at areas of interface hepatitis and in portal macrophages, whereas it was not present in non-diseased livers or other chronic inflammatory liver diseases (Table 4).[89] Approximately 20% of liver infiltrating lymphocytes express CCR9, compared to less than 2% in the livers of organ donors or patients with other chronic inflammatory liver diseases.[89] Cells expressing both α4β7 and CCR9 adhere significantly better to hepatic sinusoidal endothelial cells than $\alpha4\beta7^+CCR9^-$ cells under flow,[39] indicating a specific role for these 'gut-homing' markers. Because both CCL25 and CCR9 are not present in livers of other chronic inflammatory diseases, including PBC and AIH, it is thought that this mechanism could be specific to PSC.

CCL28 - CCR10

CCL28 expression is low in normal liver, but enhanced considerably in patients with PSC or other chronic liver diseases (PBC, HCV and ALD), especially in the presence of the ductular reaction (*i.e.* cholangiocyte, hepatocyte or hepatic progenitor cell proliferation into reactive bile ducts in response to liver injury).[90] Expression is most abundant on biliary epithelial cells, but also on portal endothelial cells and to a lesser extent on sinusoidal endothelium (Table 4).[52] A subset of liver infiltrating T cells expressing its receptor CCR10, co-expresses integrin αEβ7 (encoded by *ITGAE* and *ITGB7*), which allows them to position in the intra-epithelial compartment via binding to E-cadherin expressed at epithelial adherens

Table 4. Chemokines and their expression in normal and PSC liver.

Chemokine	Normal liver	PSC liver
CXCL12	Bile ducts in portal tracts	Enhanced expression in interlobular and septal bile ducts
CCL20	Biliary epithelial cells	Increased in biliary epithelial cells
CCL21	Portal endothelium, Dendritic cells	Increased on portal endothelium and small vascular channels
CCL25	Not expressed	Hepatic sinusoidal endothelium
CCL28	Low amounts	Bile ducts Reactive bile ducts Portal and sinusoidal endothelium Macrophages

PSC, primary sclerosing cholangitis.

junctions.[52] Apart from the aforementioned pro-inflammatory mechanisms, CCL28 expression by biliary epithelial cells could also provide a signal to attract CCR10 positive Tregs to the inflamed portal tracts in order to dampen inflammation.[52] Although a small proportion of CCR10$^+$ T cells that infiltrate the liver in PSC co-express gut-homing integrin α4β7, and CCL28 is also able to trigger α4β7-dependent lymphocyte arrest on MAdCAM-1, CCL28's specific role in PSC-IBD still remains to be determined.[91]

CXCL12 - CXCR4

CXCL12, also called stromal cell-derived factor 1 (SDF-1), is a chemokine that binds to its specific receptor CXCR4 as well as to atypical chemokine receptor 3 (ACKR3). In normal liver, CXCL12 is expressed on bile ducts in portal tracts, whereas this expression is greatly enhanced and also present in interlobular and septal bile ducts in different liver diseases, including PSC, PBC and AIH.[92] Migration and adhesion assays showed that CCR9$^+$ liver infiltrating lymphocytes preferentially migrate to CCL25 rather than CCL5 or CXCL12, but CXCL12 did elicit chemotaxis of PSC liver-derived lymphocytes.[89] This suggests that CXCL12 may play a role in retaining CCR9$^+$ lymphocytes around bile ducts via co-expression of CXCR4, rather than in recruiting these lymphocytes into the liver.[89]

VAP-1

VAP-1 is an adhesion molecule expressed by endothelial cells in the liver with dual properties: it has amine oxidase activity and supports leukocyte recruitment to sites of inflammation.[50] Two ligands have been described for VAP-1; Siglec-9, expressed on granulocytes and monocytes, and Siglec-10, expressed on B cells, monocytes and eosinophils (Table 1).[93,94] In the absence of inflammation, VAP-1 is expressed in extrahepatic vessels throughout the body, however during inflammation, it is upregulated in the large and small intestine where it mediates T-cell binding to mucosal vessels.[95] Enzymatic activity of VAP-1 generates products including aldehyde, ammonia and H_2O_2 that can induce NF-κB-dependent expression of different adhesion molecules in the gut and liver including VCAM-1 and ICAM-1, and more specifically, MAdCAM-1 expression on endothelial cells *in vitro* and *ex vivo* in human samples and *in vivo* in mice.[82,96,97] In PSC livers, as well as in other immune-mediated liver diseases, VAP-1 is highly expressed compared to non-diseased liver, most prominently on the endothelial lining of the sinusoids (Table 2).[52,97] Additionally, VAP-1 expression is markedly present on fibrotic septa and the walls of portal/septal vessels of cirrhotic livers from patients with PSC, co-localising with α-smooth muscle actin (αSMA) and stromal cells within fibrous septa.[97] It has been proposed that in patients in the early stages of PSC-IBD, colonic inflammation leads to an increased burden of amine release from both bacteria and inflamed epithelium via the portal circulation to the liver. This would lead to an increase in amine oxidase activity via VAP-1, driving upregulation of adhesion molecules including MAdCAM-1, which causes recruitment of α4β7$^+$ mucosal T cells leading to a pro-inflammatory response.[97] However, the increased expression in fibrous septa and αSMA-positive cells in various cirrhotic liver diseases could indicate that this is not disease specific, but has a more general role in influencing tissue fibrogenesis.[98]

E-cadherin - αEβ7

Cell-adhesion molecule E-cadherin is constitutively expressed by hepatocytes and biliary epithelial cells (Table 2).[99] Nakagawa *et al.* identified a loss of E-cadherin expression in biliary epithelial cells from PSC livers compared to normal livers, and demonstrated that E-cadherin loss in the biliary epithelium favours periportal inflammation in mice.[99]

The β7 integrin is only present in 2 heterodimeric integrins, α4β7 and αEβ7.[100] The heterodimer integrin αEβ7 is predominantly expressed on mucosal T lymphocytes and dendritic cells, where it mediates retention of lymphocytes in or near the epithelium via interactions with E-cadherin expressed on epithelial cell membranes (Table 2).[23] As expected, a higher proportion of liver-derived CD3$^+$ lymphocytes than peripheral blood CD3$^+$ T cells were αEβ7 positive in patients with PSC.[23] TGF-β, which is highly present in fibrotic tissue, has been shown to increase the expression of *ITGAE* and *ITGB7* mRNA, whereas it decreases *ITGA4* (gene encoding for α4) mRNA levels.[101] This has led to the hypothesis that α4β7$^+$ T cells could differentiate into αEβ7$^+$ T cells

Key point

Chemokines CCL25, CCL28 and CXCL12 are present in PSC livers, contributing to infiltration and positioning of T cells in the liver.

within the liver tissue under the influence of TGF-β, which is locally secreted by epithelial cells.[101] In murine small intestine, adhesion of αE to epithelial E-cadherin is promoted by CCL25, suggesting that the interaction between CCR9 and CCL25 plays a role.[102] In PSC livers, where CCL25 is aberrantly expressed, this interaction could also be present.

Therapeutic options using lymphocyte trafficking mechanisms

Thus far, there is still no recommended medical therapy for PSC according to European and American guidelines.[103,104] Ursodeoxycholic acid is widely prescribed, but despite more than 20 years of research has not been proven to modify the disease course.[105] Currently, therapy is in fact limited to treatment of complications such as dilatation of dominant strictures and liver transplantation in case of end-stage liver failure. Therefore, finding a medical treatment for PSC is an urgent unmet need. In the past decade, several novel agents interfering with gut-homing immune cells have emerged. However, to date, studies have mainly focused on IBD. Blocking lymphocyte trafficking to the bile ducts could be a potential mechanism to reduce inflammation and halt disease progression in PSC.

Vedolizumab

Vedolizumab is a humanised monoclonal antibody that specifically targets integrin α4β7. When vedolizumab binds to integrin α4β7, the antibody-integrin complex is internalised into the cell within 24 hours, rendering binding to MAdCAM-1 and fibronectin impossible.[86,106] The efficacy of vedolizumab in IBD was demonstrated in several placebo-controlled phase II and III clinical trials of patients with moderately active UC as well as moderately active CD, and it has also been shown to be effective during long-term follow-up.[107–110] Vedolizumab was licensed for the treatment of CD and UC in 2014. The potential efficacy and safety of vedolizumab for the treatment of PSC-IBD has only been evaluated in small, retrospective studies and case reports (Table 5). Treatment with vedolizumab was shown to be efficient with regard to the intestinal inflammation in patients with PSC-IBD.[111,112] However, these series showed conflicting results regarding changes in alkaline phosphatase levels as a surrogate endpoint for liver disease activity.[111,113–115] It must be noted that there were different limitations in these studies. The studies consisted of small numbers and heterogeneous groups, including both patients with and without ursodeoxycholic acid treatment, which could dampen the effect of changes in alkaline phosphatase. Furthermore, both pre- and post-transplant patients were included, as well as patients with different disease stages. More detailed analysis of these preliminary data as well as prospective trials using sufficient numbers and follow-up time are warranted.

Key point

Vedolizumab as a treatment option for patients with PSC-IBD has thus far only been evaluated in retrospective series, showing conflicting results regarding changes in alkaline phosphatase levels (used as a surrogate for liver disease activity).

Abrilumab

Abrilumab (AMG181/MEDI7183), which is a fully human monoclonal antibody against α4β7, has been investigated for the treatment of moderate to severe CD, where it showed moderate beneficial effects for remission and response.[116] A phase IIb trial for moderate to severe UC demonstrated a favourable safety and efficacy profile in patients with UC,[117] however, to date, there has been no data reported on patients with co-existent PSC.

Etrolizumab

Etrolizumab is a monoclonal antibody against β7, selectively blocking both binding of integrin α4β7 to MAdCAM-1 as well as αEβ7 to E-cadherin. It has been investigated in a randomised phase II trial for UC, where it showed potential beneficial results, and phase III trials are currently underway.[118] Inhibition of β7 could be less gut-specific than inhibition of α4β7, since αEβ7 is expressed in different tissues throughout the body. It is not yet clear whether αE-expressing dendritic cells are blocked by etrolizumab, which could also affect priming of gut-homing T cells. Whether etrolizumab could influence liver infiltrating T cells in patients with PSC has not been investigated yet.

Anti-MAdCAM-1

Recently, 2 phase II randomised, double-blind, placebo-controlled trials investigating the efficacy and safety of an anti-MAdCAM-1 antibody (ontamalimab, SHP647, PF-00547659) for the treatment of UC and CD have been completed. It showed that ontamalimab was safe and well tolerated, as well as superior to placebo for induction and remission in patients with moderate to severe UC.[119] In CD no significant differences between study drug and placebo were found.[120] Given the finding that MAdCAM-1 is aberrantly expressed in PSC livers, treatment with this compound could have potential benefit for patients with PSC. In the previous studies, patients with liver disease were excluded from the programme, so no data on PSC-IBD are available.

VAP-1 inhibition

In 4 different animal models of liver injury, inhibition of VAP-1 reduced recruitment of leukocytes and improved fibrosis.[98] Currently, a single-arm, 2-stage, open-label, multicentre phase II clinical trial is being conducted, in which the safety and activity of timolumab (BTT1023), a fully human, monoclonal antibody against VAP-1, is being investigated in patients with PSC.[121] To date, no data on efficacy are available.

Other compounds

Natalizumab was the first antibody developed to interfere with gut-homing. It targets the α4

Table 5. Current studies investigating vedolizumab treatment for PSC.

Ref.	Study type	Patients, n	Primary outcome	Population	Results
Lim *et al.* Inflamm Bowel Dis 2016	Case series	10	Clinical and biochemical intestinal response after 7 months	PSC-IBD, AISC-IBD, Pre- and post-LT	• Clinical response in 40%, significant decrease in fecal calprotectin ($p = 0.03$) and QOL ($p = 0.03$) • FU too short to comment on effect on pre-LT flares or post-LT recurrence
Westerveld *et al.* BMJ Case reports 2017	Case report	1	Changes in liver biochemistry and MRCP imaging after 13 months	PSC-UC	• Improvement of stricturing on MRCP • Decrease in ALP (225 IU/L to 127 IU/L), ALT (121 IU/L to 64 IU/L) and AST (69 IU/L to 42 IU/L)
Christensen *et al.* Al Pharmacol Ther 2018	Retrospective cohort study	34	Change in serum ALP at week 14 and week 30	PSC-IBD Pre- and post-LT	• No -overall change in ALP levels at week 14 or week 30 ($p = 0.35$ and $p = 0.99$, respectively)
Caron *et al.* ECCO 2018	Retrospective cohort study*	54	Decrease ≥ 50% serum ALP at week 30	PSC-IBD	• Decrease of at least 50% from baseline to week 30 in 4 patients (7.4%)
Doherty *et al.* ECCO 2018	Retrospective cohort study*	44	Changes in liver biochemistry at 8, 24 and 36 weeks	PSC-IBD Pre- and post-LT	• Significant rise in ALP levels at week 8, 24 and 36 in PSC-IBD patients ($p = 0.033$, $p = 0.005$, $p = 0.028$ respectively)
Tse *et al.* Al Pharmacol Ther 2018	Retrospective cohort study	27	Changes in hepatic biochemistries and radiographic changes after 14 months	PSC-IBD	• No significant change of ALP levels after 14 months ($p = 0.24$) • No significant decreases in AST, ALT, bilirubin or radiographic changes ($p = 0.98$, $p = 0.99$, and $p = 0.70$, respectively)
Lynch *et al.* Clin Gastroenterol Hepatol 2019	Retrospective cohort study	102	Changes in liver biochemistry at day 42 and last follow-up	PSC-IBD	• ALP drop by > 20% in 20.6% of patients at last FU • Rise in mean ALP, ALT and bilirubin from baseline to last FU ($p \leq 0.05$, $p \leq 0.01$ and $p \leq 0.001$ respectively)

AISC, autoimmune sclerosing cholangitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; FU, follow-up; IBD, inflammatory bowel disease; LT, liver transplantation; PSC, primary sclerosing cholangitis; QoL, quality of life; MRCP, magnetic resonance cholangiopancreatography; QoL, quality of life; UC, ulcerative colitis.

* Data from abstracts presented at international congresses, no full manuscript available yet.

integrin, thereby blocking both binding of α4β7 to MAdCAM-1, as well as α4β1 to VCAM-1. After approval of natalizumab for CD, a report of progressive multifocal leukoencephalopathy due to activation of the JC virus (human polyomavirus 2) was published, which was attributed to inhibition of α4β1 dependent homing via VCAM-1 in the central nervous system.[122] The use of natalizumab for CD is only registered in the US. Cilofexor, a non-steroidal farnesoid X receptor (FXR) agonist, has recently been tested for the treatment of PSC in a phase II study, in which it led to significant improvement in liver biochemistries and markers of cholestasis.[123] Its potential interference with lymphocyte trafficking was shown in mice, in which treatment with obeticholic acid, another FXR agonist, showed a reduction of α4β1 expression on both T and B cells in the spleen.[124] Another homing-interfering small molecule, which has been studied in IBD was vercirnon (CCX282-B), a CCR9 antagonist. Clinical studies for the treatment of CD did not demonstrate efficacy.[125] There are no data on natalizumab, nor vercinon, for patients with PSC.

Conclusions

In the past decade, gradual steps towards unravelling the aberrant gut-homing hypothesis have been taken. The proposed mechanism involving recruitment of gut-primed T cells expressing integrin α4β7 towards the liver in PSC is influenced by expression and upregulation of several adhesion molecules and chemokine receptors. Although there are some differences in lymphocyte subsets present in the small intestine and colon of patients with PSC-IBD, no significant differences involving chemokines or adhesion molecules have been observed in the gut, specifically for PSC-IBD compared to IBD in general. This suggests that the origins of the aberrant gut-homing in PSC should likely be sought in the liver. Fig. 1 presents a putative overview of which factors may play a role in this aberrant homing.

It must be noted that virtually all of the data comes from observational studies. In order to advance our understanding, given the lack of a proper inflammatory animal model of PSC, clinical trials of compounds that interfere with these homing mechanisms are warranted to really tease out which pathways/cell types matter in causing and/or maintaining portal inflammation in PSC.

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Please refer to the accompanying ICMJE disclosure forms for further details.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Supplementary data

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