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EDITORIAL

Role of chemokines and their receptors in viral persistence and liver damage during chronic hepatitis C virus infection

Juan R Larrubia, Selma Benito-Martínez, Miryam Calvino, Eduardo Sanz-de-Villalobos, Trinidad Parra-Cid

Juan R Larrubia, Eduardo Sanz-de-Villalobos, Liver Research Unit, Department of Gastroenterology, Guadalajara University Hospital, University of Alcalá, Donante de Sangre st. 19002 Guadalajara, Spain
Selma Benito-Martínez, Miryam Calvino, Trinidad Parra-Cid, Liver Research Unit, Guadalajara University Hospital, University of Alcalá, Donante de Sangre st. 19002 Guadalajara, Spain
Author contributions: Larrubia JR and Benito-Martínez S contributed equally towards the conception and design of the review; Larrubia JR wrote and revised the manuscript; Calvino M, Sanz-de-Villalobos E, and Parra-Cid T contributed equally to the supportive work and supervision.
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Correspondence to: Juan R Larrubia, MD, MSc, PhD, Department of Gastroenterology, Guadalajara University Hospital, University of Alcalá, Donante de Sangre st. 19002 Guadalajara, Spain. jlarrubiam@meditex.es
Telephone: +34 -949-209200 Fax: +34-949-209259
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Abstract

Chemokines produced in the liver during hepatitis C virus (HCV) infection induce migration of activated T cells from the periphery to infected parenchyma. The milieu of chemokines secreted by infected hepatocytes is predominantly associated with the T-helper/T-cytotoxic type-1 cell (Th1/Tc1) response. These chemokines consist of CCL3 (macrophage inflammatory protein-1α; MIP-1α), CCL4 (MIP-1β), CCL5 (regulated on activation normal T cell expressed and secreted; RANTES), CXCL10 (interferon-γ–inducible protein-10; IP-10), CXCL11 (interferon-inducible T-cell α chemoattractant; I-TAC), and CXCL9 (monokine induced by interferon γ; Mig) and they recruit T cells expressing either CCR5 or CXCR3 chemokine receptors. Intrahepatic and peripheral blood levels of these chemokines are increased during chronic hepatitis C. The interaction between chemokines and their receptors is essential in recruiting HCV-specific T cells to control the infection. When the adaptive immune response fails in this task, non-specific T cells without the capacity to control the infection are also recruited to the liver, and these are ultimately responsible for the persistent hepatic damage. The modulation of chemokine receptor expression and chemokine secretion could be a viral escape mechanism to avoid specific T cell migration to the liver during the early phase of infection, and to maintain liver viability during the chronic phase, by impairing non-specific T cell migration. Some chemokines and their receptors correlate with liver damage, and CXCL10 (IP-10) and CXCR3 levels have shown a clinical utility as predictors of treatment response outcome. The regulation of chemokines and their receptors could be a future potential therapeutic target to decrease liver inflammation and to increase specific T cell migration to the infected liver.

Key words: Chemokines; Chemokine receptors; Hepatitis C virus; Viral hepatitis pathogenesis; Persistent infection; Viral escape mechanism

Peer reviewers: Dr. Deborah L Diamond, Department of Microbiology, University of Washington, Box 358070, Seattle, WA 98195-8070, United States; Dr. Markus Reiser, Professor, Gastroenterology-Hepatology, Ruhr-University, Bochum, Bürkle-de-la-Camp-Platz 1, Bochum 44789, Germany

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INTRODUCTION

The hepatitis C virus (HCV) is a hepatotropic non cytopathic virus very efficient in evading the host immune response. Hepatitis C infection is a major cause of chronic liver disease worldwide, affecting at least

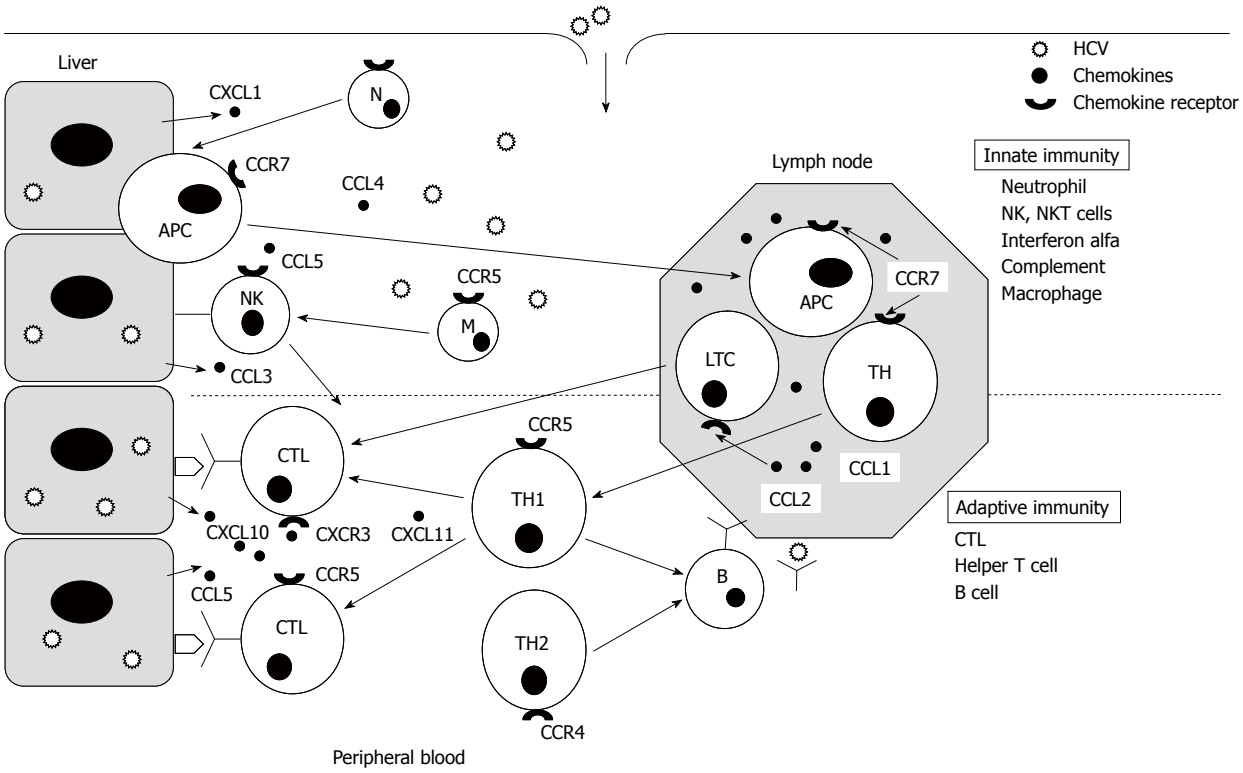

Figure 1 Innate and adaptive immune response. Importance of specific cytotoxic T cell response. In a non-cytopathic viral infection the development of a vigorous specific cytotoxic T lymphocyte (CTL) response is essential. Professional antigen presenting cells (APC) take up viral antigens and migrate from infected parenchyma to the lymph nodes to prime naive specific CTLs. These cells express the chemokine receptor CCR7 to reach the lymph nodes, attracted by CCL1 and CCL2 chemokines. After priming, specific CTLs lose CCR7 expression and up-regulate CCR5 and CXCR3 chemokine receptors, then migrate to the hepatic parenchyma to develop their effector function, attracted by the chemokines produced in the liver. During the early phase of infection, innate immunity is the first barrier for fighting against the virus. The cellular innate response is also recruited in the infected parenchyma by the interaction between chemokines and their receptors.

170 000 000 people[1]. Approximately three quarters of infected subjects develop a chronic infection, but only one third progress to cirrhosis, hepatocellular carcinoma and liver failure without treatment[2]. Nowadays around 50% of patients treated with pegylated-interferon plus ribavirin clear the virus[3,4]. To control HCV infection an adequate specific T cell response is necessary[5-7], with T cells that are able to migrate to the infected site to develop their effector functions (Figure 1). Nevertheless, specific T cells fail to remove the virus in the majority of patients[7,8], because often a non-specific T cell population is recruited to the infection site, and these cells are presumably responsible for the chronic damage[9] (Figure 2).

In both scenarios the attraction of leukocytes to the liver is controlled by chemokines, which are chemotactic cytokines secreted by infected cells and interact with their receptors expressed on the recruited leukocytes[10] (Figure 3). In an experimental model of influenza virus infection, the importance of appropriate chemotaxis to control viral infection was shown. In this model, cytotoxic specific CD8+ cells expressing inadequate chemokine receptors were not able to reach the infected site and clear the virus, while specific cytotoxic T cells expressing the correct chemokine receptors controlled the infection without tissue damage[11] (Figure 4). On the other hand, it has also been demonstrated that chemokines and their receptors can be involved in liver damage. In an animal model study it was reported that a massive hepatic infiltration by non-specific T cells, expressing chemokine receptors associated with the type-1 response, can cause acute liver failure[12] (Figure 5). Therefore, chemokines and their receptors are associated with viral control but are also associated with immune-mediated liver inflammation. Moreover, in a hepatotropic viral infection in humans, a huge intrahepatic non-specific mononuclear infiltrate during viral persistence was noticed, while this was not present in subjects with viral control[13] (Figure 2). In this last study, the intrahepatic chemoattraction of non-specific T cells perpetuated the liver damage. Consequently, also in humans, chemokines and their receptors develop an important role in viral clearance and in the development of chronic tissue inflammation. Obviously, the modulation of these pathways is important for generating an efficient immune response, and for participating in the inflammatory process during the chronic infection phase, but pathway modulation could also be a viral strategy used by HCV to escape from immune control[14]. This review introduces the advances obtained in the last decade on the role of chemokines and their receptors in chronic hepatitis C pathogenesis.

STRUCTURE AND FUNCTION OF CHEMOKINES AND THEIR RECEPTORS

Table 1 Chemokines and their receptors

	Chemokine receptor	Chemokine ligands	Target cells
Subfamily CC			
	CCR1	CCL3, CCL5, CCL7, CCL14	T cells, monocytes, basophils and eosinophils
	CCR2	CCL2, CCL8, CC7, CCL13, CCL16	Memory T cells, monocytes and dendritic cells
	CCR3	CCL11, CCL13, CCL7, CCL5, CCL8, CCL13	Eosinophils, basophils, mast cells, T helper 2 cells and platelets
	CCR4	CCL17, CCL22	T helper 2 cells, dendritic cells, basophils, macrophages and platelets
	CCR5	CCL3, CCL4, CCL5, CCL11, CCL14, CCL16	T cells, monocytes
	CCR6	CCL20	T cells, B cells and dendritic cells
	CCR7	CCL19, CCL21	T cells and dendritic cells
	CCR9	CCL25	T cells, plasma cells
	CCR10	CCL27, CCL28	T cells
Subfamily CXC			
	CXCR1	CXCL8, CXCL6	Neutrophils and monocytes
	CXCR2	CXCL8, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6	Neutrophils, monocytes and vascular endothelial cells
	CXCR3-A	CXCL9, CXCL10, CXCL11	T helper 1 cells, mast cells and mesangial cells
	CXCR3-B	CXCL4, CXCL9, CXCL10, CXCL11	Neoplastic cells and vascular endothelial cells
	CXCR4	CXCL12	Expressed in multiple cells
	CXCR5	CXCL13	B cells and T helper cells
	CXCR6	CXCL16	CD8+ cells, natural killer cells and memory CD4+ cells
Subfamily CX3C			
	CX3CR1	CX3CL1	Macrophages and smooth muscle cells
Subfamily XC			
	XCR1	XCL1, XCL2	T cells and natural killer cells

Chemokines are small heparin-binding proteins that direct the movement of mononuclear cells through the body to contribute to the development of an adaptive immune response and to the pathogenesis of inflammation. These molecules also play a role in angiogenesis, haematopoiesis, lymphoid organ development, wound healing and regulation of embryonic development. These proteins are 8-10 kDa in size with 20%-70% amino acid sequence homology and are secreted by resident cells at the inflammatory site[10]. Around 50 chemokines have been described and are subdivided into four families according to the position of the two N-terminal cysteine residues: CXC, CC, XC and CX3C[15,16,17] (Table 1). The CXC family has also been subdivided into two groups depending on the presence of the ELR motif (Glu-Leu-Arg). A systematic nomenclature has been adopted in the past few years for chemokines and their receptors[18,19]. Chemokines induce cell migration and activation by binding to specific G-protein-coupled cell-surface receptors on target cells, called chemokine receptors[10] (Table 1). Receptor triggering leads to a cascade of cellular activation, including the generation of inositol triphosphate, the release of intracellular calcium, and the activation of protein kinase C[20]. Chemokine receptor signalling also activates small guanosine triphosphate binding proteins of the Ras and Rho families[21]. Rho proteins are involved in cell motility through regulation of actin-dependent processes such as membrane ruffling, pseudopod formation, and assembly of focal adhesion complexes[15]. All these mechanisms propel cells in the appropriate direction. In humans different chemokine receptors subdivided into four families have been described: XC, CXC, CC and CX3C chemokine receptors. These receptors are expressed on different types of leukocytes, and some are constitutively expressed while others are induced, depending on the degree of leukocyte activation and differentiation[15]. Polarisation of chemokine receptor expression on T cells depending on the cytokine production profile has been demonstrated[22]. Chemokine receptors, such as CCR5 and CXCR3, are associated with the type-1 response, while CCR3, CCR4 and CCR8 are associated with the type-2 response[23,24,25,26]. Due to the preferential Th1/Tc1 response of liver infiltrating T cells during chronic hepatitis C[27,28], this review focuses on these two chemokine receptors, which bind chemokines from the non-ELR-CXC and CC subfamilies. The ligands for CXCR3 are interferon (IFN)-γ-inducible protein 10 (IP-10, CXCL10), monokine induced by IFN-γ (Mig, CXCL9), and IFN-inducible T-cell α chemoattractant (I-TAC, CXCL11). CXCR3 is expressed on activated T cells and natural killer cells[29]. The CCR5 ligands comprise regulated upon activation, normal T-cell expressed and secreted (RANTES, CCL5), macrophage inflammatory proteins 1α (MIP 1α, CCL3) and 1β (MIP 1β, CCL4). CCR5 is expressed predominantly on activated and memory T cells. Hereafter the systematic nomenclature for chemokines will be used.

CHEMOKINE SECRETION AND CHEMOKINE RECEPTOR EXPRESSION IN CHRONIC HEPATITIS C

The migration of lymphocytes to the liver is a complex process involving adhesion, rolling, triggering, and transendothelial migration. Chemokines and their

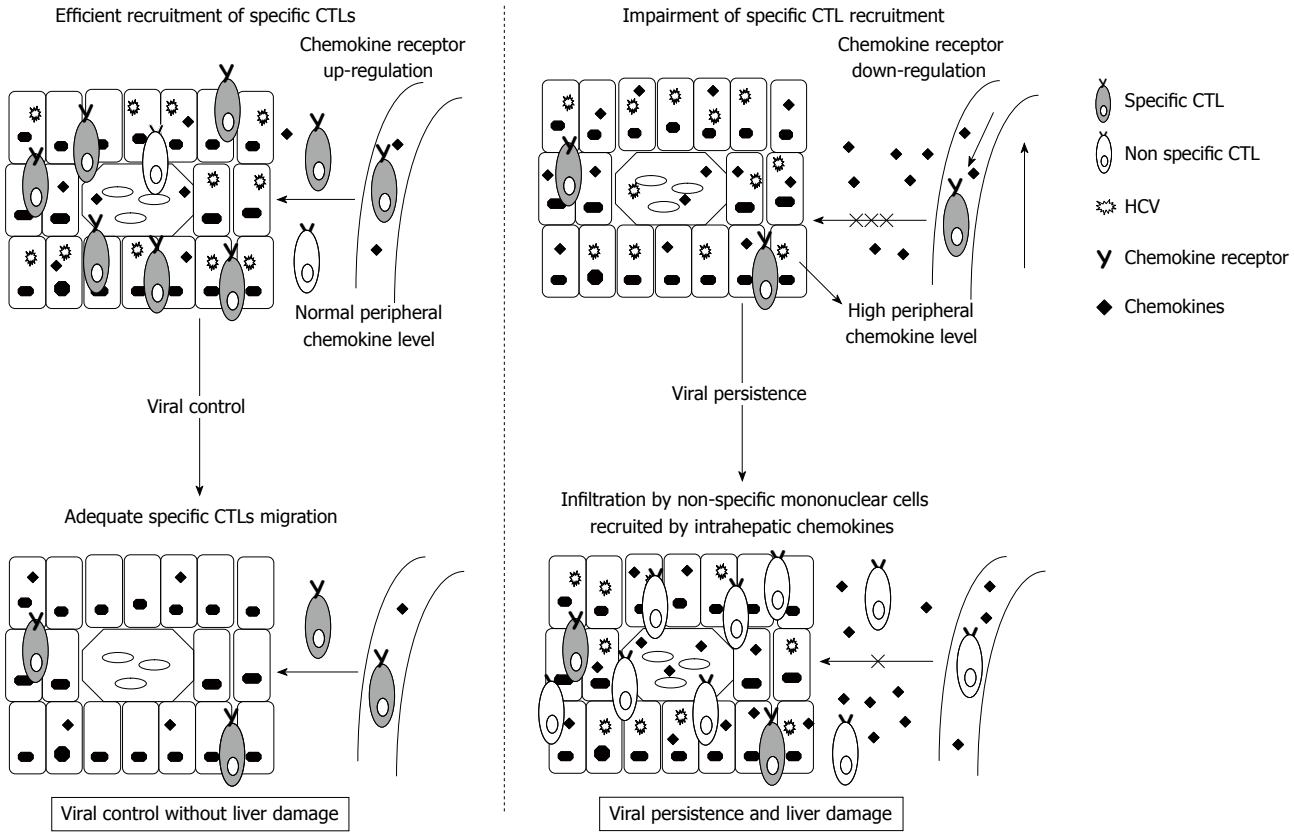

Figure 2 Different migration potential between resolved and persistent HCV infection. In a resolved infection HCV-specific cytotoxic T lymphocytes (CTL) migrate rapidly to the infected liver, attracted by the chemokines produced by hepatocytes, succeeding in controlling HCV infection without liver damage. In persistent infection the migration of T cells to the liver may be impaired. High chemokine levels during infection may induce chemokine receptor down-regulation on T cells by molecule internalization. This mechanism could impair the migration of specific T cells during primary infection, which could inhibit HCV clearance. During the chronic phase, the persistent presence of HCV in the liver could keep a long-standing chemokine production, which could attract non-specific mononuclear cells to the liver, and be responsible for chronic liver damage. The relative migration impairment due to chemokine receptor down-regulation on non-specific T cells could modulate inflammatory infiltration of the liver, inducing chronic low-grade liver damage, which could favour host and virus long-term survival.

receptors play an essential role in this multistep pathway[30,31]. In chronic hepatitis C, the expression of different chemokines in the liver has been described. CXCL10 is increased in the liver and peripheral blood during chronic hepatitis C[32,33,34,35]. This molecule is produced by hepatocytes and sinusoidal endothelial cells[33,34]. CXCL9 and CXCL11 are also increased in the serum and liver of subjects with chronic hepatitis C[33,36]. CXCL9 is detected primarily on sinusoidal endothelial cells, while CXCL11 is produced mainly by hepatocytes[33,37]. The intrahepatic expression of CCL5 is also elevated in chronic hepatitis C and it is produced by hepatocytes, sinusoidal endothelial cells and biliary epithelium[37]. Finally, several studies have reported an increased level of CCL3 and CCL4 either in the liver or in serum. These molecules are detected on endothelial cells, on some hepatocytes and on biliary epithelial cells[33,35,38]. The expression of all these chemokines in the liver can be induced directly by HCV. Previous reports have shown a high hepatocyte synthesis of CXCL10, CXCL9 and CCL5, induced by some HCV proteins such as NS5A and core[39], although a recent *in vitro* study suggests that HCV proteins could also decrease the expression of CCL5 and CXCL10 genes[40]. All these chemokines recruit T cells with a Th1/Tc1 phenotype expressing specific chemokine receptors such as CCR5 and CXCR3[24]. The non-ELR-CXC chemokine attracts CXCR3 expressing T cells while CC chemokine attracts CCR5 expressing T cells to the liver. Consequently, in chronic hepatitis C, an intrahepatic enrichment of CCR5 and CXCR3 expressing T cells, located in the hepatic lobule and portal tracts, has been shown while these populations are very infrequent in uninfected subjects[33,35,37] (Figure 6).

CORRELATION BETWEEN LIVER INFLAMMATION AND CHEMOKINE/ CHEMOKINE RECEPTOR

Persistent HCV infection is characterised by a non-specific inflammatory infiltrate in the liver, mainly composed of CD8+ cells[41,42], and responsible for liver damage[9]. These cells are attracted by the interaction between the intrahepatic secreted chemokines and the chemokine receptors expressed on T cells. Previous reports have shown a correlation between liver inflammation and liver infiltrating CXCR3/CCR5 expressing T cells[35,37] (Figure 7). The frequency of occurrence of these cells was positively correlated with portal and lobular inflammation but not with liver fibrosis. These data suggest that CCR5 and CXCR3

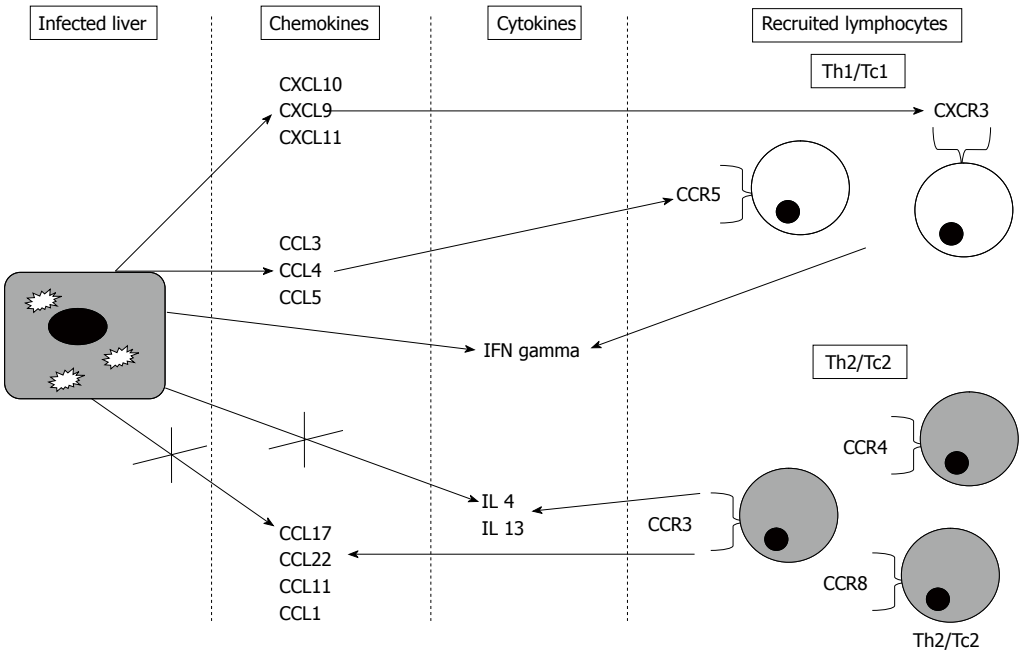

Figure 3 Chemokines and chemokine receptors related to chronic hepatitis C pathogenesis. In chronic hepatitis C, intrahepatic chemokines recruit Th1/Tc1 cells expressing CCR5/CXCR3 chemokine receptors. The X symbol indicates that chemokines and cytokines associated with a Th2/Tc2 response are not primarily produced in the HCV infected liver.

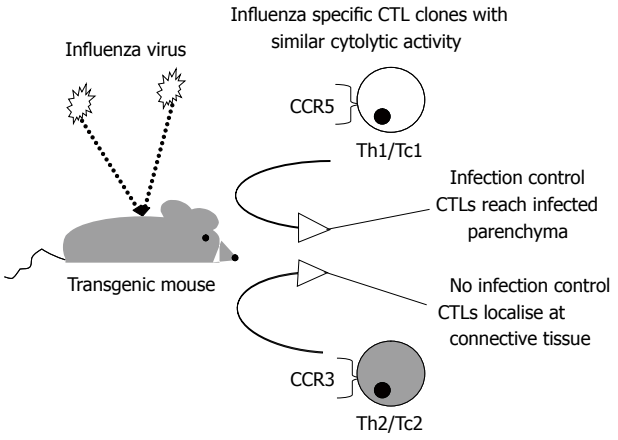

Figure 4 Adequate chemotaxis is necessary to control a viral infection. Specific cytotoxic T cells with active *in vitro* effector functionality are not able to control a viral infection if they do not express the appropriate chemokine receptor to reach the infected parenchyma. In a murine model of influenza virus infection, specific CCR5-expressing T cells were able to clear the virus while administration of specific CCR3-expressing T cells induced mouse death. CTLs: cytotoxic T lymphocytes.

could play an important role in chronic liver damage by means of recruitment of inflammatory T cells into the liver. Several previous studies have also shown a correlation between liver inflammation and chemokine levels. Intrahepatic CXCL10 mRNA levels are associated with intralobular inflammation[43]. Similarly, CXCL9 and CXCL11 correlate with the grade of liver inflammation[37,44]. Furthermore, CC chemokines are also correlated with intrahepatic inflammatory activity[45]. Clearly, intrahepatic CCL5-positive cells correlate with inflammatory activity but not with liver fibrosis[37]. The absence of correlation between liver fibrosis and liver infiltrating CXCR3/CCR5 expressing T cells and their ligands could be due to a statistical beta error, but also could suggest that it is necessary for something other than liver inflammation to occur in order to develop fibrosis, such as genetic and non-genetic factors[46]. Nevertheless, a recent study, examining a large sample of chronic hepatitis C patients, showed a positive correlation between CXCL9, CXCL10 and CXCL11 intrahepatic levels and the grade of fibrosis[47], indicating that persistent liver inflammation produced by the mononuclear cells attracted by these chemokines could finally induce the activation of a liver fibrosis cascade. Bearing in mind all the previous data, it is possible to speculate that chemokines are secreted in the infected liver to attract an adaptive immune response able to clear the virus. Unfortunately, when the specific response fails these chemokines also attract non-specific T cells, which are not able to remove the virus but produce liver inflammation (Figure 2). Therefore, as chemokines are nonspecific chemoattractants, the intrahepatic inflammatory infiltrate produced during chronic infection is mainly non-HCV-specific and consequently unable to eliminate HCV. It is, however, able to produce cytokines capable of initiating and perpetuating hepatic fibrogenesis[48]. The efficiency of this mechanism could play a role in determining why chronically infected individuals either do or do not progress to fibrosis. Certain polymorphisms in key chemokines known to be up-regulated in chronic HCV, such as CCL5, have been identified as correlates with the development of fibrosis[49].

MODULATION OF CHEMOKINE/CHEMOKINE RECEPTOR PATHWAY AS A VIRAL ESCAPE MECHANISM

HCV is usually able to evade the immune system efficiently. Several HCV escape mechanisms have been previously described, such as selection of escape mutations, induction of specific T cell anergy or resistance to the effects of α-interferon[5,50]. One

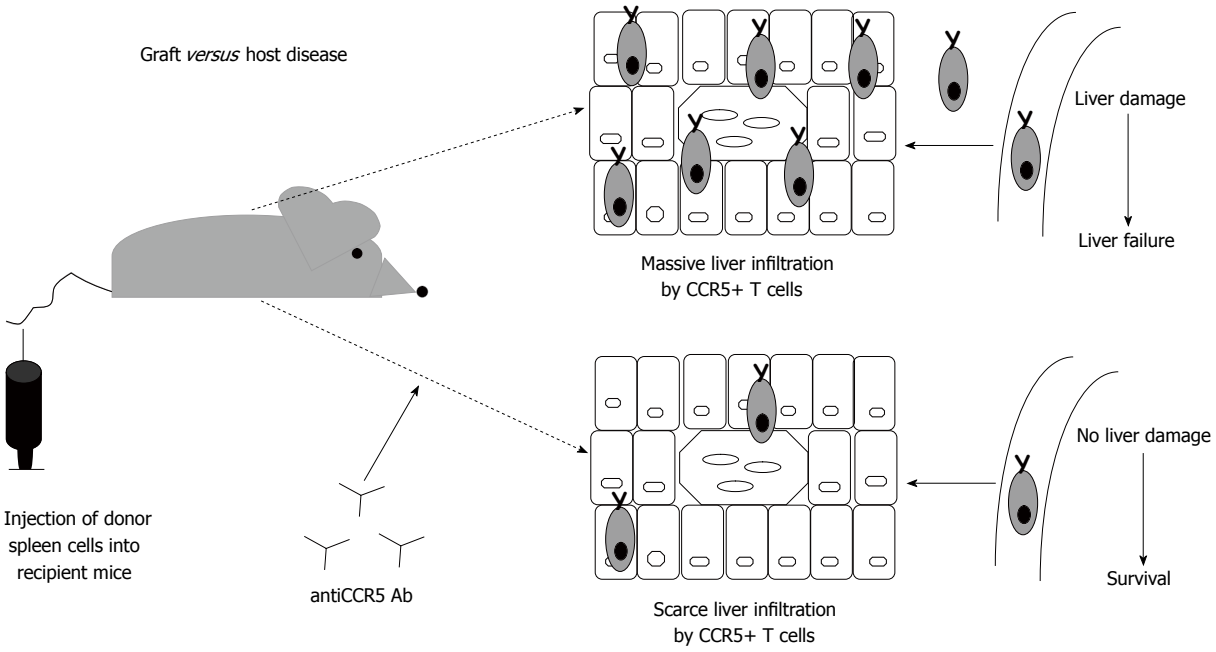

Figure 5 Intrahepatic chemoattraction of non-specific T cells causes liver damage. In a murine model of graft *versus* host disease the liver is infiltrated by CCR5-expressing T cells causing liver failure. This process can be blocked by using anti-CCR5 monoclonal antibodies.

hypothetical mechanism for HCV to survive could be to reduce hepatic chemotaxis of T lymphocytes to impair infection control during primary infection and also to decrease tissue damage during the chronic phase. The natural history of chronic hepatitis C means it can take up to three decades to develop liver cirrhosis[51]. This in turn means that the immunologically-mediated liver damage must be continuous but very light. For HCV it is essential to extend host survival as much as possible to assure its own viability. Considering these facts, it could be important for HCV to impair the expression of chemokine receptors associated with the type-1 response to improve its survival ability.

One mechanism to achieve this could be to reduce T cell migration into the liver through impairment of CCR5 and CXCR3 expression. To maximise the ability of the immune system to control the infection, a high frequency of HCV-specific CCR5+/CXCR3+ T cells should be expected during primary infection. Soon after HCV infection, prominent CD8+ cell responses are repeatedly observed and transient up-regulation of CCR5 and CXCR3 expression is seen[52,53]. During chronic hepatitis C, however, T cells show reduced surface expression of chemokine receptors associated with the Th1/Tc1 response while an intracellular increase of these molecules has been described[54]. This finding suggests the occurrence of HCV-mediated chemokine receptor internalization in chronically infected subjects. Moreover, a high serum concentration of CCL3 and CXCL10, associated with a normal or reduced peripheral frequency of CCR5- and CXCR3-positive T cells during chronic hepatitis C, has been also described[35,54]. During chronic HCV infection, the observed absence of an increase in the number of peripheral CCR5/CXCR3-positive T cells could be due to either an intrahepatic sequestration of CCR5/CXCR3 expressing T cells, caused by CCL3/CXCL10 attraction, or to a down-regulation of these chemokine receptors produced by the high serum concentration of their ligands.

It has been shown that GB virus C, a close relative of HCV[55], can reduce CCR5 expression on T cells by inducing CCL5 release[56,57]. This mechanism impairs the ability of HIV to infect CD4 T cells, thus extending host survival[57,58]. Another study into HCV infection described CCR5 down-regulation on CD8+ cells by receptor internalization[54]. It has been shown that the HCV-E2 protein, after binding to CD81[59], induces CCL5 secretion by CD8+ cells and the ensuing interaction between CCL5 and CCR5 is responsible for CCR5 down-regulation on these cells[60]. All these data suggest that HCV could modulate chemokine receptors associated with the Tc1 response to achieve a survival advantage. This mechanism could decrease HCV-specific T cell migration during acute infection, avoiding viral control, and could also impair non-specific T cell migration during persistent infection, modulating liver inflammation and fibrosis which could extend host and viral survival. If HCV is able to interfere with CCR5/CXCR3 expression, an increase in T cells expressing these chemokine receptors after viral load drop due to anti-viral treatment should be expected, together with a CXCL10/CCL3 decrease. To address this significant issue, a longitudinal analysis of CCR5/CXCR3 expressing CD8+ cells and CXCL10/CCL3 levels during treatment was performed[35]. In the majority of treated patients in this study, an increase in CCR5/CXCR3 expressing CD8+ cells was demonstrated. This finding was associated with a significant decrease in CXCL10 and CCL3 serum levels after 24 wk of treatment. A likely explanation for these data is that HCV control

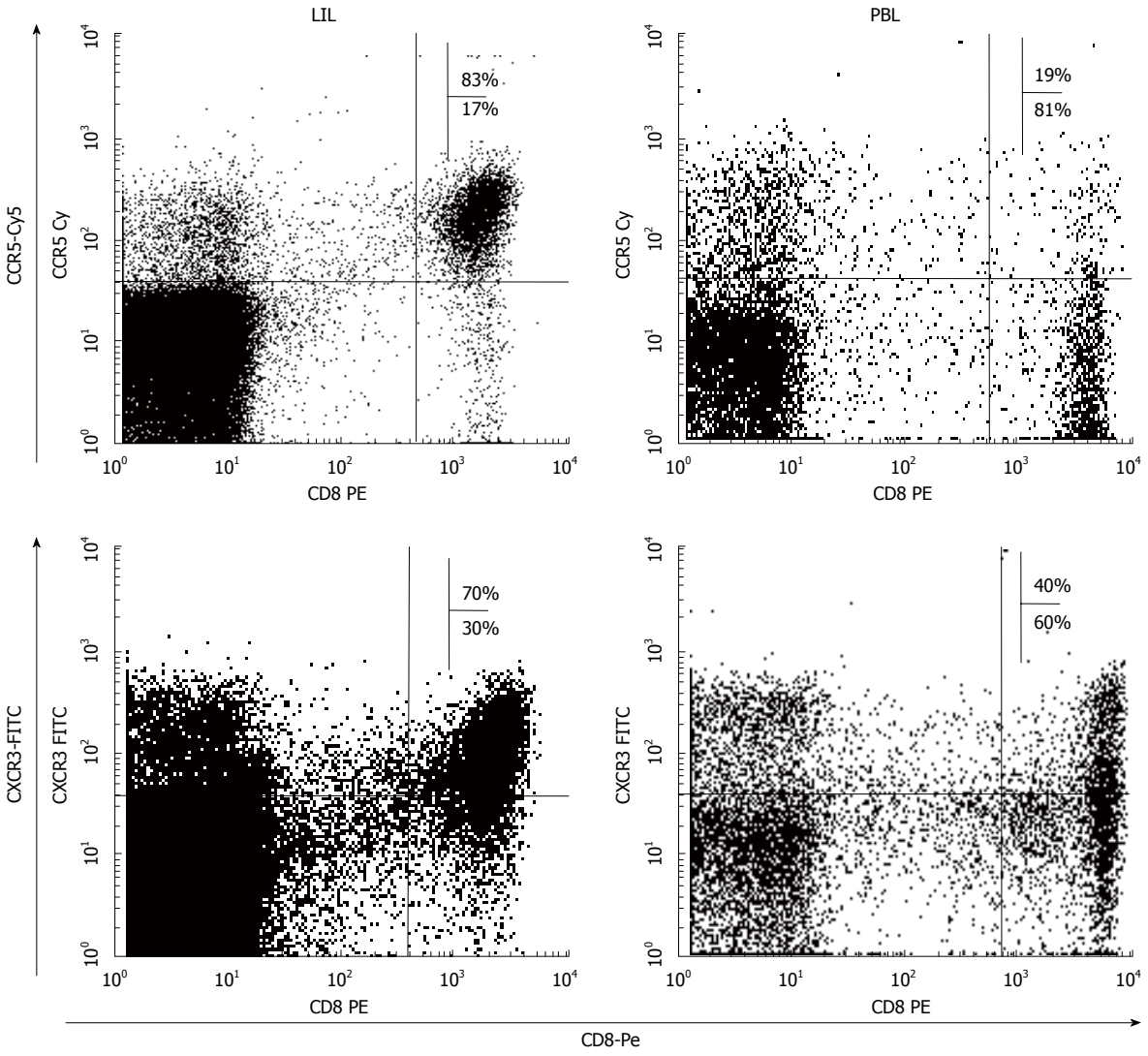

Figure 6 Intrahepatic enrichment of CCR5 and CXCR3 expressing T cells. FACScan® dot-plots of liver infiltrating (LIL), and peripheral blood (PBL) lymphocytes from a patient with chronic hepatitis C stained with labelled antibodies against CD8, CCR5 and CXCR3. The intrahepatic frequency of CCR5/CXCR3-expressing CD8+ cells is higher than in the peripheral blood.

during treatment could decrease CXCL10/CCL3 release, allowing CCR5/CXCR3 up-regulation on peripheral CD8+ cells. Actually, in this study a significant positive correlation between HCV viral load and CCL3 and an almost significant correlation with CXCL10 was shown. In summary, all these data taken together suggest that HCV could down-regulate CCR5 and CXCR3 expression on T cells by means of the secretion induction of their chemokine agonists. This strategy could favour HCV escape from immune control and could also decrease long-standing liver inflammation, allowing extended host and virus survival.

CHEMOKINE/CHEMOKINE RECEPTOR LEVELS AS TREATMENT RESPONSE OUTCOME PROGNOSTIC TOOL

As previously commented, Tc1/Th1 associated chemokines and their ligands can be modulated by HCV infection to impair the immune response. Therefore, the levels of these molecules may also influence treatment-mediated viral clearance. Previous studies have shown how baseline CXCL10 serum concentration is associated with the outcome of antiviral therapy in monoinfected[61-64] patients and in patients co-infected with HIV[65]. Elevated pre-treatment CXCL10 levels correlate with non-response to current therapy. Moreover, it was shown that the increase in CXCR3 expressing CD8+ cells during treatment is associated with SVR[35]. This suggests that for HCV, it is important to modulate the expression of this receptor not only to maintain liver viability but also to escape from immunological control. In addition, in this last study, a faster reduction in CXCL10 serum concentration was suggested in responders than in non-responders during the first 12 wk of treatment. Therefore, high CXCL10 may decrease the response of CXCR3 expressing T cells and have a negative influence on treatment outcome. Patients with either low base-line or rapid decrease of CXCL10 levels could promptly restore the response of CXCR3 expressing T cells which could assist in viral control. On the other hand, the absence of an increase in CXCR3

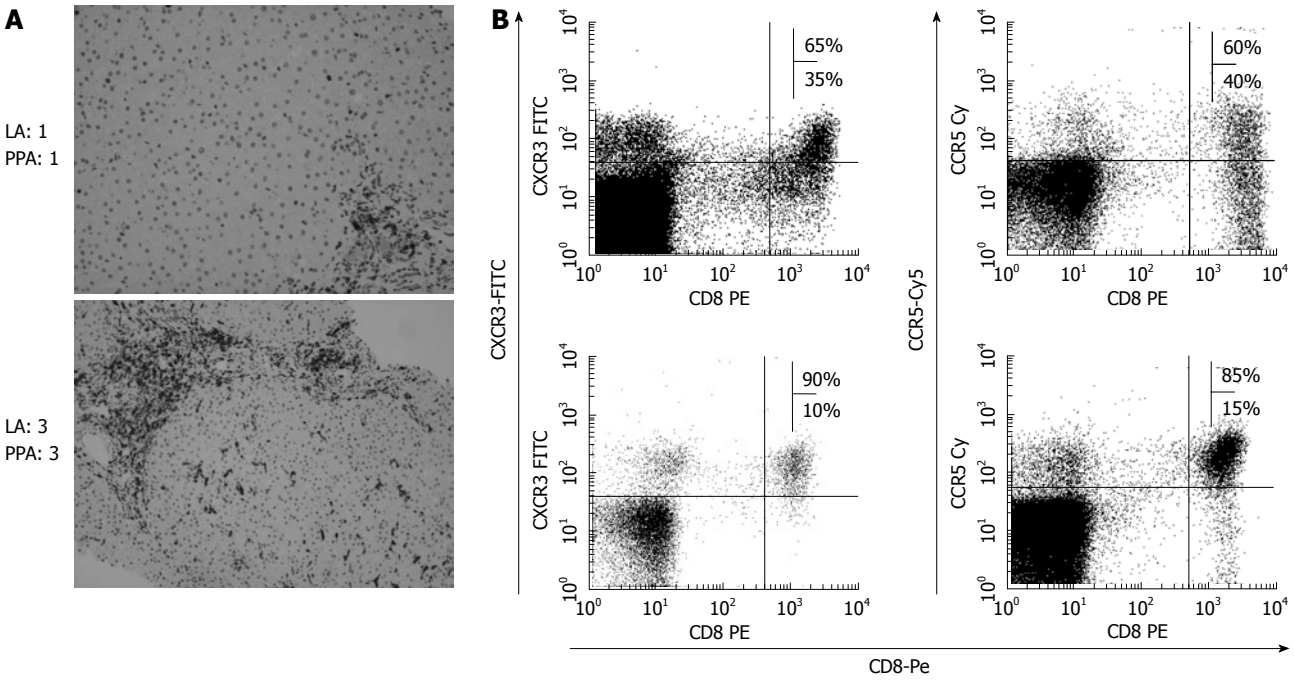

Figure 7 Correlation between liver inflammation and frequency of intrahepatic CCR5 and CXCR3 expressing T cells in chronic hepatitis C. A: Representative photomicrographs of liver immunostaining for CD8 from two chronic hepatitis C patients with different grades of inflammation. CD8 cells are stained in dark by the immunoperoxidase technique. Original magnification 400X. A patient with lobular activity (LA) 1 and porto-periportal activity (PPA) 1 showed little staining while a patient with LA 3 and PPA 3 presented intense CD8 staining; B: FACScan® dot-plots of intrahepatic lymphocytes from these two patients after staining with CD8-Pe and with either CCR5-Cy5 or CXCR3-FITC mAbs. In the upper right quadrant are represented the double positive cells. The frequency of CCR5/CXCR3 expressing CD8+ cells is higher in the patient with the higher histological liver inflammation.

expressing CD8+ cells after 24 wk of treatment is associated with a 100% negative predictive value of SVR[35]. This information may be clinically important in predicting non-response and allowing the termination of treatment in those patients with no increase in the frequency of CXCR3 expressing CD8+ cells after 24 wk of treatment. Nevertheless, with these data it is impossible to completely rule out the possibility that the observed change in chemokine patterns during treatment was an epiphenomenon due to a direct interferon effect[66]. This aspect could be clarified by studies based on patients treated with protease inhibitors. Finally, CCL20 and CXCL9 have also been suggested as tools to predict treatment outcome[61,67]. All these studies defined to predict treatment response provide preliminary information only since they are based on a very small number of patients. Therefore, these data should be re-confirmed by larger multivariate studies before applying these prognostic variables to daily clinical work.

ROLE OF CHEMOKINE/CHEMOKINE RECEPTOR POLYMORPHISMS

Several chemokine and chemokine receptor polymorphisms have been associated with different HCV infection outcomes. A CXCL11 polymorphism, defined by a 5-bp deletion in the CXCL11 promoter, has been associated with an increased risk of chronic HCV infection[68]. The distribution frequency of the allele was found to be significantly increased in a chronically HCV infected population compared to healthy controls. This deletion variant significantly reduced the transcriptional activity of the CXCL11 promoter in vitro in the presence of replicating HCV, which impaired T cell migration in vivo. Moreover, a CCR5 frameshift mutation, called CCR5-Δ32 that abrogates CCR5 expression also favoured HCV infection[69]. In this study an association between this homozygous mutation and an increased prevalence of HCV infection, as well as an increase in viral load, was documented. On the other hand, this mutation has also been associated with reduced liver inflammation[49,70,71]. These data suggest that the specific and non-specific T cell migration impairment due to the absence of CCR5 expression could favour HCV persistence and could also decrease liver damage. Similarly, a CCL5 deletion mutation which produces higher expression of CCL5 is associated with a lower grade of liver inflammation and fibrosis[70,71]. In this case the CCL5 over-expression may lead to CCR5 internalization and subsequent impairment of T cell migration. These mutations, which reduce chemokine receptor expression, are interesting proofs of the role of these molecules in the development of intrahepatic inflammation during chronic hepatitis C.

CHEMOKINE RECEPTORS AS A POTENTIAL THERAPEUTIC TARGET

Human monoclonal antibodies against CCR5, CXCR3 and their ligands have been used to treat different inflammatory and infectious diseases in humans and in animal models. CCR5 monoclonal antibodies have

been shown to be effective in avoiding T cell infection by CCR5-tropic HIV-1[72,73,74], and also in decreasing tissue inflammation in some animal models[75]. CXCL10 blocking is a successful treatment for experimental colitis[76,77]. Anti-CXCR3 monoclonal antibodies display an anti-inflammatory effect in an animal model of arthritis[78] and could also be a therapeutic target in inflammatory bowel disease[79]. These molecules have not been yet tested in chronic hepatitis C, due to the absence of an adequate animal model for proving their efficiency and safety. In the near future, an HCV permissive mouse model reconstituted with a human immune system will allow us to study mechanisms of chemokine/chemokine receptor immunopathogenesis[80]. Nevertheless, in a murine model of liver failure the administration of anti-CCR5 monoclonal antibodies has been shown to suppress intrahepatic liver inflammation, allowing mouse survival[12] (Figure 5). At least theoretically, all these previous data suggest that antibodies able to block the interaction between CCR5/CXCR3 and their ligands could decrease chronic liver inflammation in HCV infected subjects unable to clear the virus. Clearly, if the migration of non-specific T cells to the infected liver is impaired, liver damage will be reduced since HCV is not directly cytopathic. This strategy could be explored in patients without a sustained virologic response after current standard treatment. These future drugs could reduce liver fibrosis progression until new effective anti-HCV treatments are available. Obviously, the lessons learnt from HIV about the safety of these drugs should be the milestone for starting clinical trials in non-responder HCV patients[81].

In summary, the current knowledge about the role of chemokines and their receptors during chronic hepatitis C strongly suggests that they are implicated in persistent liver inflammation. Moreover, HCV seems able to modulate the expression of some chemokine receptors through the induction of their ligands. This strategy could be used by HCV as a survival mechanism. First of all, it could impair specific T cell migration to the infected liver during the primary infection, weakening HCV clearing. Later, the mechanism could interfere in non-specific T cell migration to the liver during the chronic phase of infection to extend host survival. From a practical point of view, some chemokines and their receptors have been shown to be prognostic tools in predicting anti-HCV treatment responses, and after new larger studies to re-confirm these data, these predictors could be added to daily clinical practice. Finally, the blocking of chemokines and chemokine receptor engagement is a therapeutic strategy that should be explored in the near future for non-responders to current anti-HCV therapy.

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