Cytokines and HCV-Related Autoimmune Disorders

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Abstract

Cytokines are intercellular mediators involved in viral control and liver damage being induced by infection with hepatitis C virus (HCV). The complex cytokine network operating during initial infection allows a coordinated, effective development of both innate and adaptive immune responses. However, HCV interferes with cytokines at various levels and escapes immune response by inducing a T-helper (Th)2/T-cytotoxic 2 cytokine profile. Inability to control infection leads to the recruitment of inflammatory infiltrates into the liver parenchyma by interferon (IFN)-γ-inducible CXC chemokine ligand (CXCL)9, -10, and -11 chemokines, which results in sustained liver damage and eventually in liver cirrhosis. The most important systemic HCV-related extrahepatic diseases—mixed cryoglobulinemia, lymphoproliferative disorders, thyroid autoimmune disorders, and type 2 diabetes—are associated with a complex dysregulation of the cytokine/chemokine network, involving proinflammatory and Th1 chemokines. The therapeutical administration of cytokines such as IFN-α may result in viral clearance during persistent infection and reverts this process. Theoretically agents that selectively neutralize CXCL10 could increase patient responsiveness to traditional IFN-based HCV therapy. Several studies have reported IL-28B polymorphisms and circulating CXCL10 may be a prognostic markers for HCV treatment efficacy in HCV genotype 1 infection.

Keywords: chronic hepatitis C, cryoglobulinemia, thyroiditis, diabetes, CXCL10, cytokines

Introduction

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV) [1].
The infection is often asymptomatic, but chronic hepatitis C infection (CHC) can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years [2].
Previous studies have revealed that 38–76% of patients with CHC develop at least one extrahepatic manifestation [1-2].
HCV may localize in several tissues out of the liver, including lymphoid tissue, kidney, skin, salivary glands, thyroid and pancreas. These tissues act as a reservoir for HCV and might contribute to the persistence and reactivation of the infection.
Replication of the virus and expression of viral proteins in extrahepatic tissues may play a role in autoimmune manifestations of CHC.
These extrahepatic autoimmune manifestations include mixed cryoglobulinemia (MC), Sjögren's syndrome, and thyroid autoimmune disorders, arthritis and lymphoproliferative disorders. HCV infection is also responsible for the production of a variety of autoantibodies including organ specific and non-organ-specific autoantibodies [1-2].

Cytokines and Chemokines

Cytokines are a broad category of small proteins that are important in cell signaling; they are released by cells and affect the behaviour of other cells. Cytokines are produced by broad range of different cells, including immune cells like macrophages, B lymphocytes, T lymphocytes, as well as by endothelial cells, fibroblasts, and various kind of epithelial cells (hepatic, thyroid, pancreas, lung, gut, etc). One cytokine may be produced by many different types of cell. They act through receptors, and modulate the balance between humoral and cell-based immune responses. They are important in host responses to infection, immune responses, inflammation, trauma, sepsis and cancer.
Over 100 different cytokines have been reported, which are classified according to their functions in subgroups: a) pro-inflammatory cytokines [interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α]; b) T-helper (Th)1

cytokines, that enhance the cellular immune response, produced by Th1 activated lymphocytes [interferon (IFN)-γ, IL-12, IL-18]; c) Th2 type cytokine which favor antibody responses, promoting B-cell proliferation and therefore antibody production (IL-10, IL-4, IL-5, IL-13); d) Th17 cytokines that are important for the differentiation of Th17 lymphocytes [IL-23, IL-6, trasforming growth factor (TGF)-β, that lead to the differentiation of Th0 to Th17 cells, which secrete IL-17A, IL-17F, TNF-α, IL-1 thus leading to pro-inflammatory reaction] [3].

Chemokines are a family of small cytokines, whose name is derived from their ability to induce directed chemotaxis in nearby responsive cells; they are chemotactic cytokines.

Small proteins (they are all approximately 8-10 kDa in size) are classified as chemokines according to the presence of four cysteine residues in conserved locations that are important for their 3-dimensional shape. Depending on the arrangement of the first two of these cysteines, chemokines are divided into four subfamilies: CXC (α), CC (β), C (γ) and CX3C (δ).

The receptors for these chemokines have been termed as CXCR, CCR, CR and CX3CR.

Functionally chemokines fall into two main categories: homeostatic, or pro-inflammatory. Homeostatic chemokines are produced constitutively; these are generally involved in lymphocyte trafficking, and localization of lymphocytes in the lymphatic system. Other chemokines are only produced during infection, or following a pro-inflammatory stimulus, and induce the migration of leukocytes to an injured or infected site; they can also activate cells to raise an immune response.

Chronic hepatitis C - Innate immunity

Activation of innate immune pathways in hepatocytes following infection leads to infiltration of pro-inflammatory, anti-viral immune effector cells into the liver [4].

Activation of cellular innate immune pathways depends upon recognition of foreign motifs of DNA, RNA, or protein [known as pathogen associated molecular patterns (PAMPs)] by innate pattern recognition receptors (PRRs). There are three PRRs families: Toll-like receptors (TLRs), “retinoic acid inducible gene 1 (RIG-I)-like receptors” (RLRs), or Nod-like-receptors (NLRs). The interplay of these receptors, and their downstream signaling pathways, determines the innate immune response. About HCV, the positive sense HCV RNA is separately recognized by two different PRRs in the hepatocyte: RIG-I and TLR3 [5].

Following the binding of this RIG-I to double-stranded, 5′ tri-phosphate RNAs containing poly-U or poly-A motif, RIG-I binds to the mitochondrial antiviral-signaling protein (MAVS) signaling adaptor [6]. TLR3 recognizes longer double-stranded RNAs (generated during viral replication) [5]. Activated TLR3 binds the signaling adaptor "Toll/IL-1 receptor (TIR)-domain-containing adapter-inducing IFN-β" (TRIF) [6].

MAVS and TRIF signaling activates various transcription factors including nuclear factor (NF)-κB, C/EBP-β, and IFN regulatory factors (IRFs), which induce gene transcription [6]. Binding sites for these transcription factors have been found in the IFN-γ-inducible protein 10 kDa (IP-10/CXCL10) promoter. HCV can induce NF-κB binding to this site in TLR3-expressing hepatoma cells [5].

Activation of IRF3 and IRF7 can lead to the induction of type I IFNs (IFN-α and IFN-β) and type III IFNs (IL-28A, IL-28B, IL-29) with anti-viral activity in hepatocytes. These secreted cytokines amplify chemokine and cytokine responses in adjacent liver cells through activation of Janus kinases (JAKs) and various signal transducer and activator of transcription (STAT) proteins [7]. Activation of JAK-STAT signaling induces IFN-stimulated genes (ISGs) through the binding of STAT dimers to IFN-stimulated response elements (ISREs) or IFN-γ activation site elements in their promoters [7]. Type II IFN or IFN-γ, a cytokine produced by infiltrating natural killer (NK) cells, CD8+ T cytotoxic (Tc) cells, and CD4+ Th1 cells, can induce STAT1-signaling through these elements [7], too. The CXCL10 promoter contains both putative ISREs and putative STAT-binding sites, and for this reason it can respond to all three types of IFN [8].

The primary cell defense mechanism in initial infection is the synthesis of anti-viral type-1 IFN [9]; IFN-α/β activates a number of intracellular mechanims that prevent viral replication and spread to other cells. However, HCV is, at least in part, unresponsive to IFN-α/β effects, and may replicates in the liver despite type-1 IFN activation, in fact, nonstructural proteins (NS) 3, NS5A, and E2 may block the expression and transcription of IFN-α/β-induced genes [10].

NK cells and NKT cells exert their anti-viral action via direct mechanisms and secretion of IFN-γ [11]. Furthermore, they allow maturation for dendritic cells (DCs) and the development of Th1/Tc 1 responses [12]. HCV can block NK cells and NKT cells functions via an interaction between HCV E2 protein and NK-cell CD81 molecule [13].

During chronic infection, HCV structural proteins can interact with TLR-2 in monocytes and induce IL-10 production, inhibiting IL-12 and IFN-α production in DCs [14], with a decrease in IFN-α production [15]. However, an increased IFN-α production in patients who fail to respond to exogenous IFN-α has been reported [16].

Some studies have shown that a progressive liver injury in CHC correlates with increased expression of Th1-associated cytokines [17].

Chronic hepatitis C - Adaptive response

HCV CD4+ T cells play a key role in adaptive response. They secrete Th1 cytokines including IFN-γ, which favors recruitment of neutrophil and macrophage and leads to inflammatory response. HCV CD4+ T cells release Th2 cytokines (IL-4 and IL-10) which limit Th1 cytokine-mediated response and induce the development of humoral response [18]. A strong and sustained, CD4+ T cell specific Th1 response is present in HCV infections evolving to resolution [19]. A weak CD4- T specific response and scarce type-1 cytokine production is observed when infection becomes chronic [20].

CD8+ Tc can clear viruses using mechanisms mediated by type-1 cytokines (IFN-γ, TNF-α), and apoptosis-related cytolytic mechanisms. In CHC specific Tc display anergic characteristics with reduced type-1 cytokine secretion [21]. Furthermore, in CHC, regulatory T cells can release IL-10 and TGF-β, inhibiting proliferation and cytokine synthesis in T cells, directly or through other cytokines [22].

T cells play a role in the regulation of humoral responses secreting cytokines: these responses cannot control CHC, however, they play a role in the pathogenesis of extrahepatic manifestations [23].

Mixed cryoglobulinemia (MC)

The hallmark of cryoglobulinemic vasculitis (CV) is the typical clinical triad (purpura, weakness, arthralgias) and multisystem organ involvement, with leucocytoclastic vasculitis, involving small and medium sized vessels. Vascular lesions are secondary to the deposition of immune-complexes, mainly mixed cryoglobulins, and complement in cutaneous and visceral organ vessels. CHC usually shows a mild clinical course, and may evolve in cirrhosis in 25% of cases; hepatocellular carcinoma is rare. The most important organ involvement is membranoproliferative glomerulonephritis type I. The typical pattern of low or undetectable C4 is commonly found. Most of the studies did not found a correlation of complement levels and cryocrit with the activity/severity of CV [24, 25].

MC is classified, according to the presence of polyclonal or oligo-monoclonal immunoglobulin M (IgMs), in type 2 and type 3, respectively. The underlying disorder of MC is the expansion of rheumatoid factor-producing B-lymphocytes; for this reason, MC is considered a 'benign' B-cell lymphoproliferative disease.

The mechanisms responsible for the MC lymphoproliferation surrounding MC remain to be investigated; it is conceivable that both genetic and/or environmental factors may influence the development of this CV.

A key factor in the pathogenesis of MC is the inhibition of the B-cells apoptosis, leading to their progressive accumulation; as suggested, by the histological characteristics of liver and bone-marrow lymphocyte infiltrates, by the high prevalence of *bcl-2* rearrangement [t(14;18) translocation], and by the regression of translocated B-cell clones after antiviral therapy [24-26].

B-Lymphocyte stimulator (BLyS) circulating levels are correlated with B-cell proliferation during CHC. These results suggest a role for BLyS in the induction and expression of B-cell proliferation [27, 28] in CHC.

Chemokine CXCL13, also known as B-lymphocyte chemoattractant (BLC), or B-cell-attracting chemokine-1 (BCA-1), is a regulator of B-cell trafficking. It has been shown [29] that up-regulation of CXCL13 gene expression is a distinctive feature of CHC: in fact, higher levels of CXCL13 in the liver, as well as in the skin of MC patients with active vasculitis, have been shown.

Interestingly, in a study [30] a reduced expression of IL-10 (a strong inhibitor of IFN-γ production) has been demonstrated in peripheral and liver T cells: suggesting that the evolution of CHC toward MC is characterized by a strong Th1 response.

An increased expression of IFN-γ [31] and IFN-γ-inducible chemokines [32] (CXCL10, -9, -11) in hepatocytes and in lymphocytes of CHC patients [33], related with the degree of inflammation, has been shown by many studies, such as an increase of circulating levels of IFN-γ and CXCL10 [2, 34].

The NS5A and core proteins, alone, or by the synergistic effect with IFN-γ and TNF-α, upregulate CXCL10 and CXCL9 gene expression and secretion in human hepatocytes [35]. These findings suggest that CXCL10 secreted by HCV-infected hepatocytes plays a key role regulating T cell trafficking into the liver tissue during CHC, by recruiting Th1 lymphocytes. Th1 lymphocytes secrete IFN-γ and TNF-α, inducing a futher CXCL10 secretion by hepatocytes, thus perpetuating the immune cascade (**Fig. 1**) [36].

More recently, it has been shown that circulating CXCL10 and CXCL11, IFN-γ-inducible (Th1) chemokines, are higher in patients with mixed cryoglobulinemia and hepatitis C (MC+HCV) than in CHC patients, overall in patients with MC+HCV in the presence of active vasculitis. Moreover, a strong correlation between circulating

IFN-γ and CXCL11 has been shown, strongly suggesting an important role of the Th1 immune response in the pathogenesis of MC [37-43].

In fact, the prototype Th2 chemokine CCL2 was not significantly different in MC patients with active vasculitis than in those without vasculitis, suggesting that the Th1 chemokine CXCL10 is specifically involved in the pathogenesis of CV [42].

The hypothesis of the importance of the Th1 chemokines in MC has been recently reinforced by other findings, that show high serum levels of CXCL9 in MC patients associated with circulating levels of IFN-γ and TNF-α [44-47].

The pro-inflammatory cytokines IL-1b, IL-6 and TNF-α have also been investigated in MC. In fact, MC patients show significantly higher circulating IL-1b, IL-6 and TNF-α than controls or HCV patients. If the importance of IL-1b and IL-6 in the immunopathogenesis of MC will be reinforced, these cytokines results could be the targets of new therapies for MC [47].

Interestingly, the proinflammatory cytokine IL-6 circulating levels were associated with high serum Th2 chemokine CCL2 [43].

On the whole, the above results suggest a complex dysfunction of the cytokine/chemokine network in MC, involving Th1 and pro-inflammatory cytokines. However, the importance of the activation of the Th1 immunity in the immunopathogenesis of CV has been shown.

Thyroid disorders associated with CHC

Many studies have, recently, confirmed an association of HCV infection with autoimmune thyroid disorders (AITD) in adults [48-50], and children [51].

The thyroid disorders observed in CHC is characterized by a higher risk of autoimmune thyroiditis (AT) in females, increased serum levels of anti-thyroperoxidase antibodies (AbTPO), and increased risk of hypothyroidism.

Recently several studies have confirmed a high frequency of AT in patients with MC and CHC [52].

In a case-control prospective study the following thyroid autoimmune abnormalities were significantly more frequent in MC+HCV patients than in HCV-negative controls: serum AbTPO, and/or anti-thyroglobulin antibodies (AbTg), and subclinical hypothyroidism [53].

The pattern of thyroid disorders in MC patients is characterized by a higher risk of AT in females, increased circulating levels of AbTPO, and increased risk of hypothyroidism, such as in CHC.

A high prevalence of papillary thyroid cancer (PTC) has been observed in patients with CHC, and more recently in MC patients, overall in the presence of AT [54-56].

The increased prevalence of PTC in CHC and MC patients is clinically relevant since about 10-30% of these patients may have an aggressive disease, requiring systemic treatments [57-59].

The immuonopathogenesis of thyroid disorders associated with CHC and MC has ben studied in many papers. Recently, it has been shown that high levels of CXCL10, CXCL9, CXCL11 are present in patients with AT, in particular in the presence of hypothyroidism, and it has been shown an involvement of Th1 immune response in the induction of AT, Graves' disease and Graves' ophthalmopathy [60-63].

Furthermore, the presence of HCV in the thyroid of chronically infected patients has been recently demonstrated [64, 65].

On these bases, it has been hypothesized that HCV thyroid infection may upregulate CXCL10 expression and secretion in infected thyrocytes recruiting Th1 cells, that secrete IFN-γ and TNF-α inducing a further CXCL10 secretion by thyrocytes, thus initiating and perpetuating the immune cascade, that leads into the appearance of AT in genetically predisposed subjects [66, 67].

This hypothesis has been recently confirmed by many studies that have found high circulating levels of CXCL10 in patients with CHC, and MC, in presence of AT [37, 39, 44, 68].

Interestingly, the fact that in MC patients circulating CXCL10 is significantly higher in presence of AT, compared to patients without thyroiditis, while CCL2 (the prototype Th2 chemokine) is comparable, suggests that the Th1 CXCL10 chemokine is specifically linked with the appearance of AT in these patients [66, 69].

Among the proinflammatory cytokines, IL-6 was modestly but significantly increased in patients with MC and AT, while IL-1b and TNF-α were not associated with the presence of AT [70].

In conclusion, the above mentioned studies show a high prevalence of thyroid disorders in patients with CHC and MC, and suggest a careful thyroid monitoring in these patients, given also the importance of thyroid metabolism in CHC patients [71].

Furthermore, these results underline the importance of the Th1 immune response in the initiation and perpetuation of AT in patients with CHC and MC, in agreement with the observations in other autoimmune disorders [72].

Cytokines and diabetes mellitus associated with HCV and MC

Many epidemiological studies since 1994 have reported that CHC is linked to diabetes [73]. The association between CHC, in patients without cirrhosis [that is a well known risk factor for type 2 diabetes mellitus (T2DM), independently form the origin of cirrhosis], and T2DM has been first shown in two studies, in patients with MC+HCV [74] and CHC [75].

In a population study (National Health and Nutrition Examination Survey-NHANES III 1988–1994) an adjusted odds ratio of 3.8 for T2DM was shown for subjects who were aged >40 years and patients with HCV [76]; furthermore, an increased incidence of T2DM has been demonstrated in patients with HCV [77].

Moreover, it has been reported that IFN treatment of CHC improves glucose tolerance [74, 78] when HCV infection is eradicated.

The above mentioned studies indicate that CHC is a risk factor for developing T2DM.

The mechanisms that have been suggested to be implicated in this higher prevalenve of T2DM in CHC are: a- insulin resistance; b- direct islet cell destruction; c- autoimmunity.

It is speculated that insulin resistance (as a consequence of hepatic steatosis) [73], and/or increased expression of TNF-α (that is strongly associated with the degree of liver diseases and insulin resistance) may lead to the development of T2DM [73].

More recently [79], it has been shown a direct cytopathic effect of HCV on the islet cells.

The type of T2DM manifested by patients with CHC is not the classical form.

Three studies have reported [74, 75, 80] that CHC patients with T2DM were leaner than T2DM controls, and showed lower LDL-cholesterol, and blood pressure. Moreover, MC+HCV patients with T2DM had more frequently non-organ-specific-autoantibodies than non-diabetic MC patients [74].

An immune-mediated mechanism of T2DM in CHC and MC patients has been postulated [74]. This hypothesis is strengthened by the finding that autoimmune phenomena in T2DM patients are more common than previously thought [81, 82]. Since the prevalence of classic B-cell autoimmune markers in patients with HCV has not been found to be increased, other immune phenomena might be involved.

On the above mentioned bases, it has been speculated that HCV infection of B-cells [83] may act by upregulating CXCL10 secretion recruiting Th1 lymphocytes, that secrete IFN-γ and TNF-α, inducing CXCL10 secretion by B-cells, thus initiating and perpetuating the immune process, that may lead to B-cells dysfunction.

This hypothesis has recently been confirmed by a study that demonstrates higher serum levels of CXCL10 in HCV patients with T2DM with respect to those without [83].

The role of cytokines in the therapy of CHC and MC

IFN-α is the cytokine commonly used in the treatment of CHC. Pegylated (Peg) IFN-α combined with ribavirin (RBV) leads to sustained viral response in 50% of patients [84]. The most important effect of IFN-α is anti-viral, however it has also an immunemodulatory action that favor Th1/Tc1 response restoration [85]. RBV, a wide-spectrum antiviral agent used in combination therapy for CHC, has immunomodulatory effects that induce type-1 IFN production [86]. A sustained viral load reduction, with antiviral drugs, has been shown to facilitate specific T response recovery and the production of type-1 cytokines in CHC [87, 88]. The administration of Th1-inducing cytokines (such as IL-12) [89], or anti-inflammatory cytokines (such as IL-10), has also been reported to reduce intrahepatic inflammation [90]; even if, such therapies remain experimental.

IL-28B

Single-nucleotide polymorphism (SNPs) near the IL-28B gene have been identified as strong predictors of both spontaneous or Peg-IFN and RBV induced clearance of HCV [91]. Several studies have shown that, in patients with genotype 1 (GT-1), rs12979860 C/C and rs8099917 T/T substitutions are associated with a more than twofold increase in sustained virological response rate to Peg-IFN and RBV treatment. Although new treatment regimens based on combination of "direct-acting antivirals" with or without IFN are in the approval phase, until combination regimens with a backbone of Peg-IFN will be used, we can expect that IL-28B holds its importance. The clinical relevance of IL-28B genotyping in treatment of patients infected with HCV genotype 2 (GT-2) and 3 (GT-3) remains controversial [91].

There is also evidence that IFN-λ3 affects the adaptive immune response.

It is known that IL-28B may induce a T-cell adaptive immune response [92]. This effect may explain the relationship between SNPs near IL-28B, adaptive response and viral clearance [93].

Clinical studies assessing safety and efficacy in the treatment of HCV with exogenous IFN-λ3 suggest that IFN-λ3 treatment inhibits HCV, however, hepatotoxicity in both healthy volunteers and HCV-infected

patients has been described [94].

CXCL10 as prognostic marker, and target

Several studies have reported that CXCL10 may be a prognostic marker for HCV treatment efficacy in HCV GT-1 infection: elevated pretreatment serum CXCL10 concentrations correlate with non-response to Peg-IFN/RBV therapy [95, 96].

Other studies have shown that IL-28B genotype and pretreatment serum CXCL10 concentrations were associated with early viral kinetics of HCV, the first phase decline or rapid virological response (RVR), as well as sustained virological response (SVR) in Peg-IFN/RBV therapy [97].

However, in a recent study in 104 Japanese genotype 1 CHC individuals treated with Peg-IFN/RBV and 45 with Peg-IFN/RBV/telaprevir, the pretreatment serum CXCL10 concentrations were not correlated with IL-28B genotype. The receiver-operator curve analysis determined the cut-off value of CXCL10 for predicting a SVR as 300 pg/mL. In multivariate analysis, the IL-28B favorable genotype and CXCL10 concentration of less than 300 pg/mL were independent factors for predicting SVR. In a subgroup of patients with the IL-28B favorable genotype, the SVR rate was higher in the patients with CXCL10 of less than 300 than in those with 300 pg/mL or more, whereas no patient with the IL-28B unfavorable genotype and CXCL10 of 300 pg/mL or more achieved SVR. Among the patients treated with Peg-IFN/RBV/telaprevir, low pretreatment concentrations of serum CXCL10 were associated with a very rapid virological response, defined as undetectable HCV RNA at week 2 after the start of therapy. This study suggests that pretreatment serum CXCL10 concentrations are associated with treatment efficacy in Peg-IFN/RBV and with early viral kinetics of HCV in Peg-IFN/RBV/telaprevir therapy [98].

Theoretically agents that selectively neutralize CXCL10 could increase patient responsiveness to traditional IFN-based HCV therapy, simultaneously reducing inflammatory immune cell activation. For example, specific inhibitors of the CXCR3A could prevent excessive activation of CD8+ Tc cells and NK cells that lead to excessive hepatocyte death, limiting Kupffer cells and hepatic stellate cells activation and delaying or preventing development of fibrosis [99].

Conclusion

Cytokines, induced by infection with HCV, are intercellular mediators involved in viral control and liver damage. A coordinated and effective development of both innate and adaptive immune responses is permitted by the complex cytokine network, that operates during initial infection. HCV interferes with cytokines at various levels and escapes immune response by inducing a Th2/Tc2 cytokine profile. IFN-γ-inducible CXCL9, -10 and -11 chemokines recruit inflammatory infiltrates into the liver parenchyma owing to the inability to control the infection process, which result in sustained liver damage and eventually in liver cirrhosis; however, fibrogenesis may also follow distinct pathways. The most important systemic HCV-related extrahepatic diseases —MC, lymphoproliferative disorders, diabetes and AITDs—are associated with a complex dysregulation of the cytokine/chemokine network and involve pro-inflammatory and Th1 chemokines. The therapeutical administration of cytokines such as IFN-α may result in viral clearance during persistent infection and reverts this process. Several studies have reported IL-28B polymorphisms, and circulating CXCL10, may be prognostic markers for HCV treatment efficacy in HCV GT-1 infection. Clinical studies assessing safety and efficacy in the treatment of HCV with exogenous IFN-λ3 are ongoing.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Figure Captions

Fig. 1 Hepatitis C virus induces the production of interferon (IFN)-γ-dependent chemokines in infected hepatocytes, endothelial cells, lymphocytes, thyrocytes and B-cells. Chemokine (C-X-C motif) ligand (CXCL)9, -10, -11 attract Th1 lymphocytes into the tissues, where they produce cytokines [IFN-α, -β, - γ and tumor necrosis factor (TNF)-α] that induce a further secretion of chemokines in cells, attracting other lymphocytes and perpetuating the immune process and inflammation.

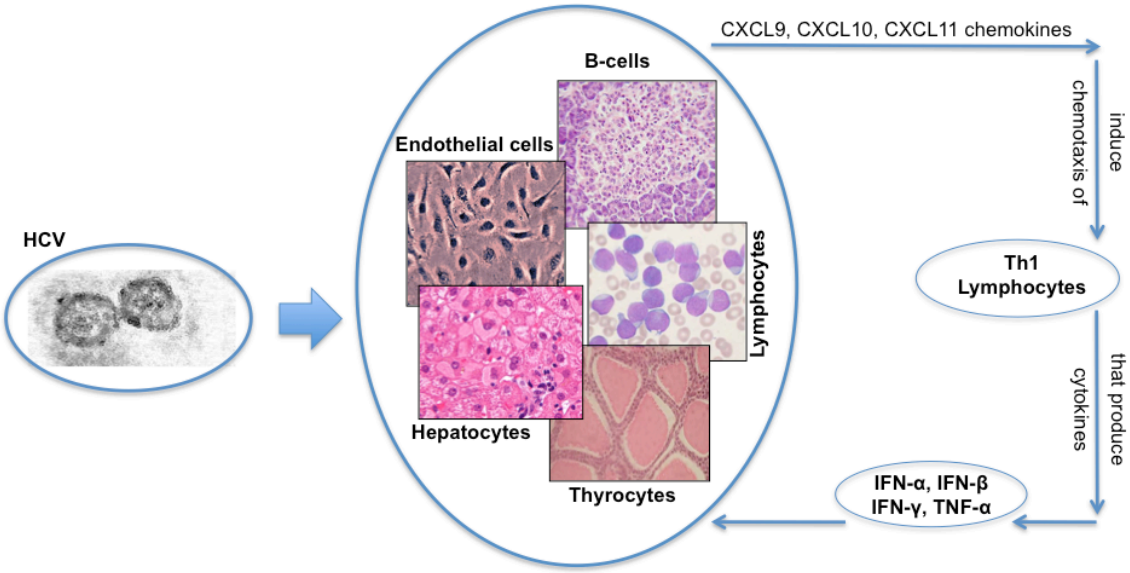
HCV
B-cells
Endothelial cells
Lymphocytes
Hepatocytes
Thyrocytes
CXCL9, CXCL10, CXCL11 chemokines
chemotaxis of
induce
Th1
Lymphocytes
cytokines
that produce
IFN-α, IFN-β
IFN-γ, TNF-α

Fig. 1