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Serum levels of Th17 associated cytokines in chronic hepatitis C virus infection

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ABSTRACT

The Th17-mediated immune response was investigated in patients chronically infected with hepatitis C virus (HCV) by determining the serum levels of the cytokines involved in the induction of the Th17 response (TGF-β and IL-6), the cytokines produced by Th17 cells (IL-17A, IL-17F and IL-22) and the cytokines whose production is stimulated by Th17 lymphocytes (IL-8 and GM-CSF). We investigated the relationships among the levels of these cytokines by assessing clinical findings, liver histology and viremia. Sixty untreated patients and 28 healthy individuals were included in the study. Cytokine levels were determined using ELISA. Differences between HCV and control groups were identified in the median levels of IL-17F (controls = 172.4 pg/mL; HCV = 96.8 pg/mL, $p < 0.001$) and IL-8 (controls = 30.1 pg/mL; HCV = 18.1 pg/mL, $p < 0.05$). IL-6 levels were higher in patients presenting moderate liver necroinflammation than in patients with mild or no liver necroinflammation ($p < 0.05$). IL-17F levels were increased in patients that had increased ALT levels. Additionally, a strong positive correlation was observed between IL-17F and IL-22 levels in the two groups investigated, and the IL-17F/IL-22 ratio was lower in the patients infected with HCV ($p < 0.0001$). Patients with low HCV viral loads had higher median levels of IL-8 (32.5 pg/mL) than did patients with high HCV loads (16.7 pg/mL, $p < 0.05$). These results suggest that in chronic hepatitis C infection, IL-17F and IL-8 could be associated with the control of liver injury and infection, respectively.

1. Introduction

Immunology studies involving chronic hepatitis C infection have been performed mainly to elucidate the immunopathogenesis and the mechanisms involved in HCV evasion of the host immune response. Although important progress has been made in these areas, the participation of Th17 cells in HCV chronic infection has not been well characterized and has been documented in only a few recent studies [1–3]. Th17 cells are a subpopulation of $TCD4^+$ cells that produce cytokines that have been described as important mediators of either autoimmunity or immune defense against bacteria, parasites and fungi, thus justifying more studies to elucidate their involvement in HCV infection. Patients chronically infected with hepatitis C virus can present extra-hepatic manifestation of autoimmunity as autoantibody production. However, this immune event has not been associated with the production of some TH17 cytokines that have been implicated in autoimmunity as IL-6, IL-17A, IL-17F or IL-22. On the other hand, recent studies have reported that cytokines as IL-17F and IL-22 could exert biological effects on hepatocellular carcinoma [4–6]. Therefore, this study investigated the serum cytokine profiles, focusing on the most important cytokines involved in Th17 immune responses, in patients with chronic hepatitis C. Furthermore, the association of serum cytokine levels with clinical and laboratory findings of autoimmunity, liver pathology and HCV viremia were investigated in these individuals.

2. Patients, materials and methods

2.1. Patients

In this study, we included 60 untreated patients with chronic hepatitis C: 28 men and 32 women, with a mean age of 47.8 ± 11.6 years (range = 25–69 years). All patients were from a hepatitis reference center in Salvador, BA, Brazil. The patients had clinical diagnosis of hepatitis C and positive serological tests for HCV infection, including indirect ELISA, detection of HCV-RNA by RT–PCR and HCV genotyping (Inno-LiPA HCV LineProbe Assay; Innogenetics, Zwijndrecht, Belgium). Co-infection with HBV, HIV

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or HTLV-I/II and the presence of bacterial or parasitic diseases were used as exclusion criteria. Blood HCV loads were determined using the AMPLICOR HCV Detection Kit v2.0 (Roche Molecular Systems Inc., Somerville, NJ, USA). The control group consisted of 28 healthy blood donors. Informed consent was obtained from all patients before participating in the study, which was approved by a local Ethical Committee.

2.2. Liver histology

Patient liver biopsies were histologically examined using hematoxylin–eosin, Picrosirius red and Perls' iron stains. The METAVIR score [7] was used to classify liver fibrosis and liver necroinflammatory activity. Liver biopsy was performed 30–90 days before the determination of serum levels of ALT, ferritin, haptoglobin, autoantibodies and cytokines.

2.3. Clinical chemistry

Serum alanine aminotransferase levels were determined using an automated test (reference value <41 U/L). Haptoglobin levels (reference value 35–195 mg/dL) were measured by nephelometry using the IMMAGE® system (Beckman-Coulter, USA), and ferritin levels (reference values 34–155 ng/mL for men and 36–262 ng/mL for women) were determined by capture immunoassay using the Access 2® system (Beckman-Coulter, USA).

2.4. Autoantibodies

Anti-smooth muscle and anti-LKM-1 antibodies were tested by IFAT using combined stomach/liver/kidney tissues (VIRO-IMMUN Labor-Diagnostika GmbH, Oberursel, Germany). Anti-phospholipid antibodies (anti-cardiolipin and anti-β2 glycoprotein) were detected by indirect ELISA (ORGENTEC Diagnostika GmbH, Mainz, Germany). IgM anti-IgG rheumatoid factor was assessed by nephelometry using the IMMAGE® system (Beckman-Coulter, USA).

2.5. Cytokine immunoassays

The serum levels of IL-6, IL-17F, IL-22, GM-CSF and TGF-β were determined using Ready-Set-Go!® ELISA kits (eBioscience Inc., San Diego, CA, USA). IL-8 and IL-17A levels were measured with ELISA kits from Bender MedSystems (Bender MedSystems, Vienna, Austria). Their analytical sensitivities were as follows: IL-6 (1.6 pg/mL), IL-8 (8.0 pg/mL), IL-17A (1.6 pg/mL), IL-17F (32.0 pg/mL), IL-22 (8.0 pg/mL), GM-CSF (8.0 pg/mL) and TGF-β (8.0 pg/mL).

2.6. Statistical analysis

The distribution of the continuous variable was determined using the D'Agostino–Pearson test. Control and HCV groups were compared using the Mann–Whitney U test, whereas three groups were compared with the Kruskal–Wallis test with Dunn's Multiple Comparison test. Proportion analysis was performed using Fisher's exact test, and the correlation between two categorical groups was analyzed using the Spearman test. Statistical significance was set at $p < 0.05$. Prism version 5.1 software was used to perform the statistical analyses (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Clinical chemistry

The median ALT level in the HCV patients was 53.1 U/L (IQR = 39.0–87.0 U/L), and a moderate increase in this enzyme was observed in 45 out of 60 (75%) patients. The median haptoglobin level was 65.0 mg/dL (IQR = 44.0–105.0 mg/dL). The median ferritin level was 149.7 ng/mL (IQR = 81.8–276.0 ng/mL). Eighteen patients (30.0%), 9 men and 9 women, had increased levels of ferritin.

3.2. Liver histology

The liver fibrosis score varied from F0 to F2 in 50 out of 60 (83.3%) patients, whereas advanced F3–F4 fibrosis was present in 10 out of 60 (16.7%) patients. Thirty-nine (67.2%) patients presented with necroinflammatory activity with scores of A0 or A1, while moderate necroinflammatory activity was observed in 19 (32.8%) subjects.

3.3. Serum cytokine levels

The serum levels of IL-17F, IL-22 and TGF-β were determined in all patients and controls; however, the levels of IL-6, IL-17A, GM-CSF and IL-8 in some patients and control subjects were below the limits of detection of the immunoassays. Thus, IL-6 levels were determined in 23 out of 60 (38.3%) patients and in 10 out of 28 (35.7%) control subjects. IL-17A levels were determined in 39 out of 60 (65%) patients and in 10 out of 28 (35.7%) control subjects. GM-CSF levels were determined in 50 out of 60 (83.3%) patients and in 26 out of 28 (92.8%) control subjects. IL-8 levels were measured in 59 out of 60 (98.3%) patients and 28 out of 28 control subjects (100%).

HCV patients displayed lower levels of IL-8 and IL-17F than did healthy controls (Table 1, $p < 0.05$). Positive correlations between IL-17F and IL-22 levels were observed in both the control group and the HCV group ($r = 0.75$, $p < 0.0001$ and $r = 0.46$, $p < 0.001$, respectively); however, the IL-17F/IL-22 ratio was higher in the control subjects than in the patients (Fig. 1, $p < 0.0001$).

Moderate positive correlations were observed between ALT levels and IL-17F or TGF-β levels ($r = 0.291$ and $r = 0.289$, respectively; $p < 0.05$). IL-17F levels were higher in patients with increased ALT than in patients with normal levels of this enzyme (Fig. 2). IL-6 and IL-22 levels did not correlate with the levels of haptoglobin or ferritin ($p < 0.05$).

3.4. Cytokine levels and liver histology

IL-6 levels were different when the groups represented by healthy controls, patients without liver necroinflammatory activity or with mild liver necroinflammatory activity (A0/A1) and patients with moderate liver necroinflammatory activity (A2) were compared (Fig. 3, $p < 0.05$). Although no difference was observed between the IL-6 levels of the healthy group and those from A0/A1 patients ($p = 0.05$), a significant difference was verified in the levels of this cytokine when the two groups of HCV patients were

Table 1
Serum levels of cytokines in healthy controls and hepatitis C patients.

Cytokine (pg/mL)	Controls	HCV	*p* Value
IL-6	3.0 (2.8–4.8)	3.0 (2.2–4.4)	>0.05
TGF-β	801 (673.5–801.0)	779.4 (688.7–868.1)	>0.05
IL-17A	3.1 (2.3–4.8)	3.2 (2.8–3.9)	>0.05
IL-17F	172.4 (114.6–232.3)	96.8 (69.8–188.1)	<0.001
IL-22	10.7 (8.8–12.8)	11.1 (9.3–17.6)	>0.05
IL-8	30.1 (17.2–77.2)	18.1 (11.9–36.2)	<0.05
GM-CSF	15.7 (11.3–22.8)	12.3 (10.5–17.3)	>0.05

Cytokine levels were determined by capture ELISA and are presented as median and interquartile range (Q1–Q3). The medians of the groups were compared by the Mann–Whitney test.

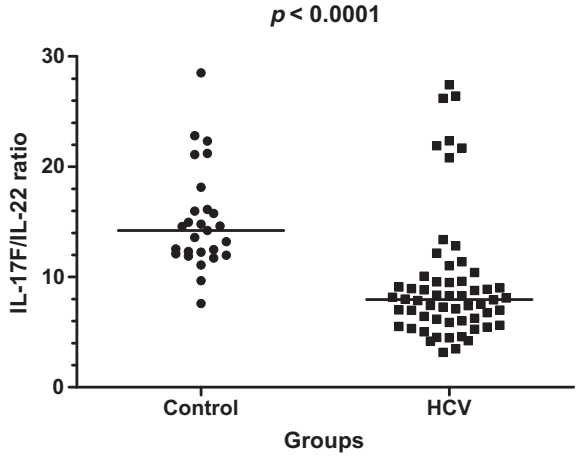

Fig. 1. IL-17F/IL-22 ratio in healthy controls and HCV patients. Horizontal lines represent the medians. The Mann–Whitney test was used to compare the medians of IL-17F/IL-22 ratios in these groups.

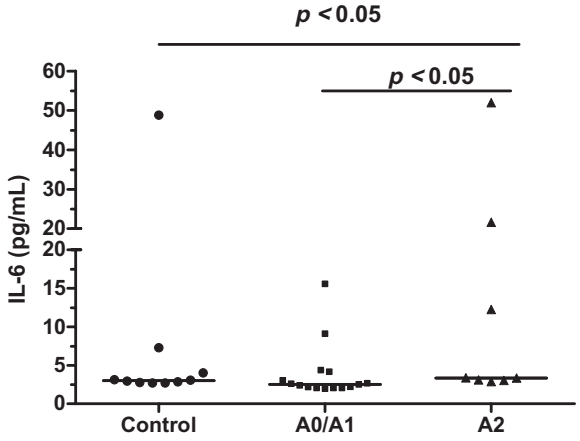

Fig. 3. Serum IL-6 levels in healthy controls, HCV patients presenting mild or no liver necroinflammation (A0/A1) and moderate liver necroinflammation (A2). Horizontal lines represent the medians. The Kruskal–Wallistest and the Dunn's Multiple Comparison test were used to compare the groups.

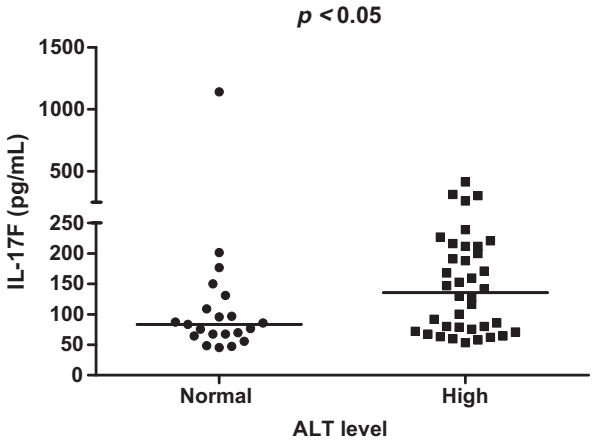

Fig. 2. Serum IL-17F levels in HCV patients presenting normal ALT level (<41 U/L, $N = 21$) or high ALT level (>41 U/L, $N = 38$). Horizontal lines represent the medians. The Mann–Whitney test was used to compare the medians of serum IL-17F levels in these groups.

compared (A0/A1 vs. A2). In contrast, no differences in serum cytokine levels were observed between patients with F0, F1 or F2 fibrosis scores and those with advanced fibrosis (F3 or F4).

3.5. Cytokine levels and autoimmunity

The presence of rheumatoid factor was observed in 33 out of 60 (55.0%) HCV patients (median level = 29 IU/mL, IQR = 23–113.5 IU/mL). Anti-smooth muscle antibodies were detected in 12 out of 60 (20.0%) patients, and anti-phospholipid antibodies were found in six out of 60 patients (10.0%); however, no differences in cytokine levels were detected in the patients that were seronegative or seropositive for these autoantibodies ($p > 0.05$).

3.6. Viral loads and cytokine levels

HCV genotype 1 infection was identified in 43 out of 60 (71.7%) patients. Twelve out of 60 subjects (20.0%) were infected with HCV genotype 3, and five out of 60 (8.3%) were infected with HCV genotype 2. Similar levels of cytokines were observed when patients infected with HCV genotype 1 were compared to those infected with HCV genotypes 2 or 3 ($p > 0.05$). Blood HCV loads were determined

Table 2
Cytokine levels in HCV patients with low or high viral load of hepatitis C virus.

Cytokine (pg/mL)	Low viral load ⩽400,000 IU/mL	High viral load >400,000 IU/mL	*p* value
IL-6	2.1 (1.8–16.2)	2.1 (2.0–19.7)	>0.05
IL-17A	3.4 (2.7–4.0)	3.2 (2.8–3.9)	>0.05
IL-17F	127.2 (75.5–226.9)	89.5 (68.2–168.1)	>0.05
IL-22	11.8 (9.5–24.4)	10.7 (9.3–17.2)	>0.05
TGF-β	787.2 (674.0–924.5)	817.6 (688.7–863.3)	>0.05
GM-CSF	12.3 (9.8–16.4)	12.2 (10.5–20.6)	>0.05
IL-8	32.5 (15.3–107.2)	16.7 (11.9–30.7)	<0.05

Cytokine levels were determined by capture ELISA and are presented as median and interquartile range (Q1–Q3). The medians of the groups were compared by the Mann–Whitney test.

in 48 out of 60 patients (80.0%): viral loads were low (⩽400,000 IU/mL) in 16 out of 48 (33.3%) patients and high (>400,000 IU/mL) in 23 out of 48 (47.9%) patients using in this classification a pre-treatment viral load cut-off previously reported [8] and adopted in our hepatitis service. The comparison of these two groups of individuals showed that patients with high viral loads had lower IL-8 levels than did patients with low HCV loads (Table 2).

4. Discussion

In this study, we investigated the involvement of the Th17 immune response in HCV chronic infection by determining serum levels of the cytokines that induce Th17 responses (IL-6 and TGF-β), the cytokines produced by Th17 cells (IL-17A, IL-17F and IL-22) and the cytokines induced by Th17 lymphocytes (IL-8 and GM-CSF).

The levels of ALT, ferritin, haptoglobin, autoantibodies and cytokines in this study were determined using the same serum sample, which was obtained from patients during their admission in the study. The short time lapse of 30–90 days between liver biopsy and cytokine level determination was important to validate the results involving liver histology and the serum levels of these immune mediators in the patients with hepatitis C. In addition, these individuals did not have co-infections and were free of immune suppression, events that could provoke fluctuation in both HCV load and cytokine levels.

The HCV patients in this study did not display elevated levels of TGF-β and IL-6. In contrast, an Indian study reported increased

serum levels of TGF-β in chronic hepatitis C infection; subjects with cirrhosis and hepatocellular carcinoma were reported to have elevated levels of TGF-β, which returned to normal levels after treatment [9]. TGF-β has immunosuppressive activity and participates in liver fibrosis by activating the transition of liver stellar cells to myofibroblast-like cells, stimulating the synthesis of extracellular matrix proteins and inhibiting their degradation. The levels of this cytokine can vary in chronic hepatitis C infection and have been associated with its clinical evolution, as changes in TGF-β are associated with progressive fibrosis [10,11]. In our study, TGF-β levels were moderately correlated with ALT levels, suggesting an association with liver injury; however, most of the patients had fibrosis scores ranging from F0 to F2, explaining the normal levels of this cytokine observed in the HCV group.

In accordance with a previous report [12], IL-6 levels were similar in HCV patients and control subjects. Increased IL-6 levels have been reported in chronic HCV patients with either non-Hodgkin's B cell lymphomas or mixed cryoglobulinemia with active vasculitis [13,12]. Our finding that IL-6 levels were unaltered in HCV patients may thus be explained by the lack of these clinical manifestations in our study population; however, the levels of this cytokine were increased in patients with moderate liver necroinflammatory activity. In addition to its participation in the liver acute phase response, IL-6 protects hepatocytes from liver injury through its anti-apoptotic effects following activation of the oncogenic protein signal transducer and activator of transcription 3 (STAT3), which also promotes hepatocellular carcinoma growth [14,15].

Although IL-17A levels and IL-22 levels were unaltered in HCV patients, IL-17F levels were lower in these subjects and were also moderately correlated with ALT levels. IL-17F is a weak inducer of proinflammatory cytokines secreted by Th17 cells that provides immune protection against infection by inducing the production of CXC chemokines, G-CSF and antimicrobial peptides [16]. In our study, IL-17F levels were strongly correlated with IL-22 levels in both control subjects and HCV patients; additionally, a significant decrease in the IL-17F/IL-22 ratio was observed in the HCV patients. IL-22 is a member of the IL-10 cytokine family that is mainly produced by Th17 and Th22^{+} cells. Expression of IL-22 is inhibited by TGF-β. IL-22 has inflammatory properties, and its expression is increased in chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. Moreover, IL-22 participates in innate immune defense by inducing liver production of acute-phase proteins, stimulating the production of LPS-binding protein (LBP) and protecting the host from liver damage by increasing the growth and survival of hepatocytes [17–21]. In this study, we detected no correlation between TGF-β and IL-22 levels. Furthermore, IL-22 levels were not correlated with the serum levels of the acute-phase proteins haptoglobin and ferritin.

The detection of similar IL-22 serum levels in control subjects and HCV patients confirms the results of a previous study that showed unaltered serum IL-22 levels in patients with viral hepatitis B or C despite the up-regulation of IL-22 expression in the livers of these individuals [2].

The observation that the IL-17F/IL-22 ratio was decreased in subjects infected with HCV merits future investigation. IL-17F down-regulates IL-6, IL-8, and vascular endothelial growth factor and inhibits angiogenesis and cancer growth, whereas IL-22 has an opposite effect, stimulating the growth of hepatocellular carcinomas through STAT3 activation, promoting metastasis and inhibiting apoptosis [22,23]. Thus, the biological significance of the IL-17F/IL-22 ratio in hepatitis C must be elucidated to evaluate its importance in liver oncology.

Although IL-6, IL-17A, IL-17F and IL-22 have been implicated in the autoimmune mechanisms of chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis and autoimmune hepatitis [5,24–29], the levels of these cytokines were similar in all of the patients, regardless of their seropositivity for rheumatoid factor, anti-smooth muscle, anti-cardiolipin or anti-β2 glycoprotein I antibodies. Therefore, this finding provides additional evidence that the seropositivity for non-organ-specific antibodies in chronic HCV infection is caused by cross-reactivity between anti-HCV antibodies and human self-antigens [30] or by the presence of natural poly-reactive autoantibodies involved in innate immune defense.

Increased serum levels of GM-CSF and IL-8 have been reported in chronic hepatitis C infection [31]; however, we did not observe similar findings in this study. In accordance with a recent study [32], although IL-8 levels were decreased in HCV subjects, the serum levels of this cytokine were higher in patients with low HCV loads than in those with high HCV loads. This finding suggests a protective role for IL-8 in the control of HCV infection and may explain the unfavorable therapeutic response of chronic hepatitis C patients with high IL-8 serum levels [33]. In summary, our results suggest that IL-17F and IL-8 could play protective roles in chronic hepatitis C infection, which seem to be associated with the control of liver injury and infection, respectively.

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