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Research Article

-137G>C Polymorphism in the Promoter Region of Il18gene is Associated with Serum Interleukin 18 (Il-18) Levels in Patients with Hepatitis C Virus Infection

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Abstract

Hepatitis C Virus (HCV) is usually associated with chronic infection and the factors leading to viral clearance or persistence are poorly understood. Interleukin 18 (IL-18) is a pro-inflammatory cytokine with broad biological effects. Several polymorphisms in the *IL18* gene and plasma IL-18 levels have been reported to influence the outcome of hepatitis C. In this study, *IL18 gene* promoter polymorphisms (-607C>A and -137G>C) and levels of serum IL-18 were analyzed in 51 HCV spontaneous clearance and 50 chronically infected patients. Single Nucleotide Polymorphisms (SNPs) were genotyped by qPCR with specific primers and a specific ELISA was used for the quantitative determination of IL-18 cytokine. The results showed that there was no evidence for association between the polymorphisms and the outcome of HCV infection. Nevertheless, plasma IL-18 levels were found to be higher in chronic HCV infected patients than in HCV clearance ones. GG genotype at position -137 was associated with higher IL-18 levels in the studied population even when adjusted for HCV infection status. In conclusion, our data suggest that -137 G>C in IL-18 gene is associated with a functional dysregulation of the IL-18 production in a Brazilian cohort of patients with HCV infection.

Keywords: IL-18; HCV; Single polymorphism and Viral clearance

Introduction

Hepatitis C Virus (HCV) infection is usually subclinical and typically asymptomatic in the acute phase. However, the virus replicates in the liver continuously and progressively and it is estimated that more than 130 million people were infected worldwide [1,2]. A hallmark of HCV infection is its high propensity to establish persistence in 60–80% of infected individuals. This patients are unable to eliminate the virus and most of them evolve to a chronic infection accompanied by liver inflammation, followed by liver fibrosis, cirrhosis and an increased risk to develop Hepatocellular Carcinoma (HCC) [3-5]. Nevertheless, some patients are able to spontaneously clear the virus. Estimates of clearance rates ranged from 20-40% [6,7] and the reasons why these differences exist in the progression of the disease are not fully understood, although the influence of host and viral factors must be considered.

The immune factors and other biomarkers associated with HCV pathogenesis are not well defined and very little is known about the early events in virus–host interactions that determine HCV clearance versus progression to chronic HCV infection. Cytokines play a key role in the regulation of immune responses. During Hepatitis C virus infection, the production of cytokine appears to contribute to viral persistence and to affect response to therapy [8-11].

One factor that can modulate the host immune response is Interleukin-18 (IL-18), also known as IFN γ–inducing factor, an important regulator of innate and adaptive immune responses that has multiple roles in chronic inflammation and autoimmune disorders [12-15]. IL-18, a member of IL-1 cytokine family, IL-18 is an 18 kDa glycoprotein synthesized as a 23 kDa inactive precursor (pro-IL-18) that needs to be cleared by caspase-1 in order to become an active [14,15,18, 21-24]. It is a pleiotropic cytokine expressed at relatively high levels in different cell types, such as macrophages, osteoblasts, monocytes, macrophages, keratinocytes, intestinal epithelial cells, astrocytes, dendritic cells and microglia [12,16-20].

The IL-18 plays a fundamental role in host defense against pathogens and can regulate both innate immunity and adaptive responses. In chronic HCV infection, the implication of IL-18 has been repeatedly proven in several studies, first as a marker of inflammation and hepatic injury and, second, as a predictor of antiviral treatment response [17,18,21,23-28]. IL-18 activity is determined in part by the action of an intrinsic inhibitor, an IL-18 Binding Protein (IL18BP), which has the ability to bind to a receptor site, preventing the action of IL-18 [15,17,22, 29-31].

The *IL18* gene is located on chromosome 11q22.2-q22.3 and a variety of single polymorphisms (SNPs) have been detected within *IL18* gene sequence. Giedraitis *et al*, [2001] described two SNPs at positions -607C>A(rs1946518) and -137G>C (rs197238). Both of them disrupt transcription factors binding sites leading to a decreasing level of IL-18 mRNA. The capacity for IL-18 cytokine production in individuals has a major genetic component. This has been related to polymorphisms within the regulatory regions of cytokine genes. Polymorphisms in *IL18*gene have been implicated in HCV infection outcome [32-35].

This study was undertaken to investigate the association of

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Table 1: Parameters and clinical laboratory measurements in the study populations.

	Clearance	Chronic HCV infection	p-value
Male	22/51 (43%)	21/50 (42%)	
Age	48.5	48	0.535
ALT (U/L)	24(16-28)	47(60.5 – 66.5)	<0.0001
AST (U/L)	23(20-28)	40(28 – 47.7)	<0.0001
FA (U/L)	73(60-101)	72.5(60.2 – 106.2)	0.986
GGT (U/L)	28(18-39)	47(25.7 – 73.2)	0.002
HCV-RNA (log)	ND	5.9	
HCV Genotype	---	1	

Laboratory data are present edinvalues medians and interquartile (25^{th}-75^{th}). Mann-Whitney test. HCV: Hepatitis C Virus; SD: Standard Deviation; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; FA: Phosphatase Alkaline; GGT: Gamma Glutamyl Transferase; ND: Not Detectable.

two SNPs in the *IL18* gene (-607C>A [rs1946518] and -137 G>C [rs187238]) and the relationship between the clearance and the persistence of HCV infection in Brazilian patients. Associations with IL-18 cytokine levels were also assessed.

Materials and Methods

Patients

A total of 101 subjects was recruited in this study, including 51 patients with anti-HCV positive and negative for HCV-RNA on at least two occasions, a minimum a six months apart, also confirmed by Recombinant Immuno Blot Assay (spontaneous clearance) and 50 with chronic hepatitis C (anti-HCV and HCV-RNA positive, with the latter being repeatedly positive over at least a 6-month period of testing) [Table 1].

The study had been approved by the local ethics committee of Clinical Hospital of the University of São Paulo under protocol 151.913 (CAPPesq) and written informed consent was obtained from each participant before sampling.

DNA extraction and analysis of cytokine polymorphisms

Total genomic DNA was extracted from whole blood samplesusing the Qiamp DNA® blood mini kit (Qiagen®, Hilden, Germany) following the protocol provided by manufacturer. All samples were typed for *IL18* gene polymorphisms (-607C>Aand -137 G>C). Genotypes weredetermined byTaqMan SNP genotyping assays (-607C>A, assay ID: C_2898460_10 and -137 G>C, assay ID: C_2408546_10 of Applied Biosystems, by Life Technologies, Foster City, CA, USA).The reactions were performed in a final volume of 25µl containing 10ng of DNA, 12.5µl of 2X TaqMan Universal PCR Master Mix (Applied Biosystems) and 1.25 µl of the SNP genotyping assay reagent (Applied Biosystems) containing primers and MGB TaqMan probes. Real-time PCR was performed in a 7500 Fast Real-Time PCR System (Applied Biosystems) under the following conditions: 10 min at 95°C, followed by 40 cycles at 95°C for 15 second and at 60°C for 1 minute.Genotyping success rate was >95%. Genotyping was repeated in 5% of subjects with 100% concordance.

Assessment of IL-18 serum

A specific ELISA (Human IL-18 ELISA Kit, MBL, Nagoya, Japan) was used for the quantitative determination of IL-18 in serum. IL-18 concentration was determined according to a reference standard curve. The detection limit was 12.5 pg/ml.

Statistical analysis

Results are expressed as mean ± SD except where stated otherwise. Continuous variables were log-transformed for the analyses when the normality of the distribution was rejected by the Shapiro-Wilk W test. Fisher's chi squared test, ANOVA and ANCOVA were used for comparisons between groups. When the normality was not verified, Mann-Whitney or Kruskal-Wallys test was selected. For the correlation analysis Pearson's r or Spearman's ρ were used. Associations with chronicity of HCV infection were assessed by regression models. Logistic regression analyses were used for cross-sectional analyses. Odds Ratios (OR) with their 95% Confidence Intervals (CI) was computed for the risk allele of each SNP in a dominant model. Adjustments for clinical and biological parameters were carried out, by including them as covariates in the regression model. Correction for multiple comparisons was performed by the Bonferroni correction method and a value of $p \leq 0.025$ was considered as significant for genotype-related comparisons. The power to detect associations of the SNPs with the chronicity of HCV infection was 0.20, for odds ratio ≥1.5 and alpha=0.05. Statistics were performed with JMP (SAS Institute Inc., Cary, NC) software.

Results

Clinical characteristics

A total of 101 patients with previous of infection by hepatitis C virus were enrolled in this study. Table 1 summarizes the demographic, virological and clinical characteristics for whole individuals included in this study, according to HCV infection state. Briefly, patients chronically infected with HCV had higher values of ALT, AST and GGT compared with patients with clearance infection, which might reflect a progression of disease and liver tissue damage. No significant difference was found between the groups regarding gender and age.

IL-18 promoter genotype and haplotype frequencies

The genotype distribution of the two groups adhered to the theoretical proportions of Hardy-Weinberg equilibrium. Genotype

Table 2: Genotype frequencies by HCV chronicity.

SNPs	Clearance	Chronic HCV infection	OR (95% CI)	p
N	51	50		
-607C>A			1.05 (0.43 – 2.58)	0.90
CC	0.275	0.260		
AC	0.549	0.580		
AA	0.176	0.160		
MAF	0.450	0.450		
-137G>C			0.87 (0.39 – 1.92)	0.74
GG	0.490	0.520		
GC	0.431	0.440		
CC	0.078	0.040		
MAF	0.293	0.260		

Single Nucleotide Polymorphisms (SNPs) are sorted in 5' to 3' order. OR (Odds Ratio) for the minor allele determined in logistic regression analyses adjusted for sex and age. MAF: Minor Allele Frequency. $p \leq 0.025$ is significant.

frequencies according to HCV infection states are illustrated in Table 2. The frequencies of chronic HCV infection for -607C>A polymorphisms (CC: 48.2%; CA: 50.9%; AA: 48.1%) and for -137 G>C polymorphism (GG: 51.0%; GC: 50.0%; CC: 33.3%). It was not possible to observe an association with the prevalence of chronic HCV infection neither with the -607C>A polymorphism (OR1.05; 95% C.I. 0.43 – 2.58; p=0.90) nor with the -137 G>C polymorphism (OR 0.87; 95% C.I. 0.39 – 1.92; p=0.74) in a dominant model of logistic regression analysis adjusted for sex and age. The CA genotype was the most common genotype among clearance and infected group in -607C>A polymorphisms. Regarding the -137 G>C polymorphism, the most frequent genotype was the GG one.

Table 3 shows the haplotype analysis performed for both polymorphisms. It was not possible to observe an association of any haplotype with the prevalence of chronic HCV infection. The linkage disequilibrium was calculated and it was possible to observe that there is moderate LD among the polymorphisms (D': 0.99; r^2: 0.47; X^2: 94.41; p<0.0001).

Plasma IL-18 concentration by clinical characteristics and genotype

The plasma concentration of IL-18 cytokine was assessed from serum samples from both HCV clearance and chronic infection individuals.IL-18 concentrations were higher in men than in women (518± 183*vs* 428 ± 201,pg/mL; mean ± SD; p=0.018) and positively correlated with ALT (r^2: 0.32; p=0.0024) and AST (r^2: 0.38; p=0.0003) levels. It was possible to observe that patients with chronic HCV infections had higher values of IL-18 when compared with patients with clearance HCV infection (536±203*vs*398± 168; pg/mL; mean ± SD; p<0.0003. Figure 1). When an ANCOVA analysis adjusted for sex and age is assessed, the same result is obtained (547 ± 25*vs* 402± 25,pg/mL; mean± SEM; p<0.0001).No genotype-related difference was observed in IL-18 concentrations regarding the -607C>A polymorphism. However, regarding the -137 G>C polymorphism, the IL-18 levels were significantly lower in patients with CCgenotype than those with GC or GG (398± 73, 440± 28 and 512± 24; pg/mL; mean ± SEM; p= 0.02. Figure 2), observed in a codominant model of ANCOVA analysis, adjusted for sex, age and HCV infection chronicity. Interestingly, when the analysis is performed by HCV infection, the association remains significantly only in the clearance group (CC: 303 ± 89, GC: 383 ± 39, GG: 433 ± 35; mean ± SEM; p=0.02) while in the HCV chronic group no association is observed (CC: 520 ± 128, GC: 497 38, GG: 591 ± 35; mean ± SEM; p=0.32).No association was observed between haplotype and IL-18 serum levels (data not shown).

Table 3: Haplotype frequencies according to HCV chronicity.

Haplotype	Clearance (n=51)	Chronic HCV infection (n=50)	OR (95% CI) Chronicity of HCV	p
CG	0.549	0.550	1.00	
CC	0.000	0.000	-	-
AG	0.157	0.190	1.18 (0.52 – 2.67)	0.69
AC	0.294	0.260	0.87 (0.44 – 1.74)	0.69

Haplotypes represent the alleles of -607C>A and-137G>C, respectively. Odds Ratios (OR) for each haplotype as compared to the odds for the most frequent haplotype (CG) Considered to be 1. Data represents the prevalence of HCV chronicity adjusted for age and sex. CI, Confidence Interval. p<0.05 is significant.

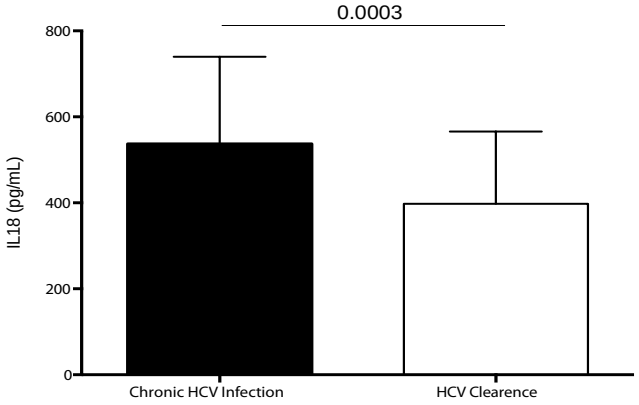

Figure 1: Serum level (pg/mL) of IL-18 in Chronic HCV infection and HCV clearance groups. Comparison level of IL-18 cytokine in serum from HCV infected patients and HCV clearance patients.

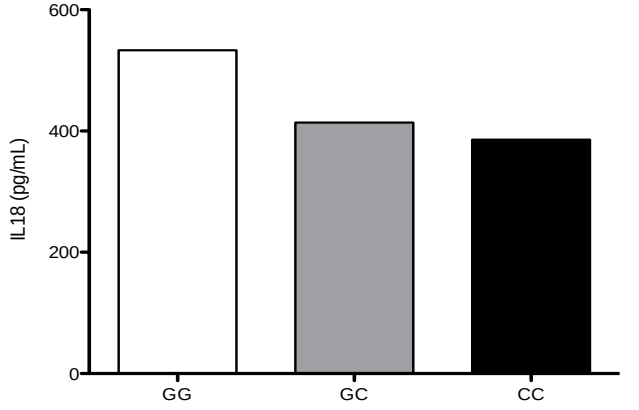

Figure 2: Impact of -137G>C polymorphisms on IL-18 levels in serum of HCV patients.
Comparison level of IL-18 cytokine in serum from HCV infected patients, according to -137G>Cgenotypes. Codominant model of ANCOVA analysis, adjusted for sex, age and type of HCV infection; p=0.02).

Discussion

HCV infection is the leading cause of chronic liver disease worldwide and may progress to cirrhosis and hepatocellular carcinoma. Among the host determinants of hepatitis C outcome the immune response and host genetic variations seen to play a major role. In HCV infection the IL-18 cytokine has been reported to be up-regulated in chronic patients [28,36,37] and another study showed the IL-18 as a marker of both inflammation and hepatic injure. Positive correlation between IL-18 level and the severity of inflammation in hepatitis C patients were also observed [21,26,38,39].

Since cytokines production varies among individuals and is associated with certain variations within coding and regulatory regions, is important to evaluate the possible associations of -607 and -137 polymorphisms in the *IL18* gene with susceptibility to HCV infection. After comparing patients who either had a persistent HCV infection or had cleared HCV infection, the present study demonstrated that two functional variants (-607C>A and-137G>C) were not associated with clearance or chronic HCV infection. These findings are consistent with previous studies that reported no differences in -607C>A and -137 G>C genotype distributions and

allele frequencies between patients and controls [21,40]. However other studies have had a different opinion about this polymorphism and the infection of HCV [32,41].

In a previous study, it was demonstrated that the -607A allele occurred more frequently in the clearance group than in chronic infection and the -137C allele was also more frequently observed in the clearance group than in chronic infection, but this difference was just observed in African American and was not observed in European American [32,41].

To validate the up-regulation of the IL-18 level in hepatitis C patients, their IL-18 serum levels were measured and compared to those of clearance. To avoid bias of serum IL-18 levels resulting from the therapy influence just untreated patients infected were included. Compared to clearance group, patients with chronic infection presented a higher increased in plasma IL-18 concentration than patients that had clear the virus. These findings confirm previous results revealing that disease progression is accompanied by an increase in plasma IL-18 and strongly support the involvement of IL-18 in causing liver injury [28,29].

A significantly increased of IL-18 levels as well as HCV-induced IL-18 production by peripheral blood mononuclear cells has been observed in the patients with chronic HCV infection [19]. Those evidences show that high IL-18 level may compromise the cellular immune response to chronic HCV infection [17].

Pro-inflammatory cytokines play a dual role in virus infection. In acute infection, these cytokines act as an antiviral and help to clear the infection. On the other hand, these cytokines may stimulate the inflammatory process in chronic infection. It was previously reported a positive correlation between higher levels of pro-inflammatory cytokines secreted in response to HCV-related liver injury, an increased necroinflammatory activity and liver fibrosis or cirrhosis [40]. Since IL-18 is a pro-inflammatory cytokine, and plays an important role in combating the invading pathogen as part of the innate immune response it was observed that elevated levels of circulating IL-18 correlate with HCV infection [27,29]. Also it was described that higher levels of IL-18 coincided with the detection of HCV RNA in the blood [39].

The relation between IL-18 polymorphisms and serum levels was assessed. The results are consistent with previous studies concerning the link between -607C>A and-137G>C polymorphisms and the decreased expression of IL-18. Giedraitis et al (2001) showed that patients who are homozygous for C at position -607 and G at position -137 have higher levels of IL-18 mRNA compared to other genotypes. Arimitsu et al (2006) demonstrated that the monocytes from -137C carriers produce a lower amount of IL-18 than from -137G carriers [33,42].

The greatest limitation of the study is the small sample size of our cohort, which might have, at least in part, affected our results. It was possible to observe an association with higher levels of IL-18 only in -137 G>C polymorphism, while no association was observed for the -607C>A. Regarding the -607C>A and the -137 G>C polymorphisms, for a minor allele frequency of 0.27 and 0.45, in the dominant model and a power of 0.80, the minimum OR detected for the prevalence of chronic HCV infection, in the present study, would be 3.2 and 3.7 respectively. So, we cannot exclude the possibility that we do not observe an association with the prevalence of chronic HCV infection, due to lack of power.

In our study although the -607 and -137 polymorphisms were not associated with the prevalence of chronic HCV infection, it was possible to observe that the polymorphism at position -137 in *IL18* gene was associated with serum levels of this cytokine. The CC genotype was observed commonly associated with individuals who have low production of the IL-18 cytokine, while individuals with GC and CC genotype were associated with intermediate and high production of IL-18. When individuals were separated by type of infection (clearance and chronic HCV infection), the association remains significantly only in clearance group. This might have occurred due to small sample size, and consequently lack of power of the study (as discussed above), or due to the fact that individuals with chronic HCV infections had values of IL-18 so high that the polymorphism's effect is not so important. Indeed, in the ANCOVA analysis patients with the C allele had lower values of IL-18 cytokine in the chronic group (data not shown) but it was not enough to reach statistical significance.

In conclusion, our data suggest that -137 G>C polymorphism in *IL18* gene is associated with the IL-18 cytokine production in the serum of patients with HCV infection, more specifically with patients with clearance HCV infection. The data indicate that -137 G>C polymorphism associates with IL-18 serum levels in clearance HCV infection, but not in chronic HCV infection, probably, because the HCV infection is a multifactorial disease and other factors also affect protein levels. More studies with larger sample size are necessary to identify if this polymorphism might be involved in the progression of hepatitis C.

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