Online Submissions: wjg.wjgnet.com
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doi:10.3748/wjg.15.3884

World J Gastroenterol 2009 August 21; 15(31): 3884-3890
World Journal of Gastroenterology ISSN 1007-9327

BRIEF ARTICLES

Endotoxin receptor *CD14* gene variants and histological features in chronic HCV infection

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Supported by A grant of the Deutsche Forschungsgemeinschaft MI 474/1-1; Askar E was supported by a scholarship from Damascus University, Syria
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Received: May 14, 2009 Revised: July 17, 2009
Accepted: July 24, 2009
Published online: August 21, 2009

Abstract

AIM: To analyze the correlation between CD14 rs2569190/C-159T single nucleotide polymorphism (SNP) and disease progression in chronic hepatitis C.

METHODS: Liver biopsy specimens from a total of 137 and 349 patients with chronic hepatitis C were separately evaluated with respect to necroinflammatory activity (grading) and architectural changes (staging). In one group, further histological lesions characteristic for hepatitis C, hepatitis C virus subtypes, and biochemical parameters of liver disease were also investigated. Samples of genomic DNA were genotyped for the respective SNP by 5'-nuclease assays using fluorescent dye-labeled allele-specific probes.

RESULTS: Genotype distribution did not deviate from the Hardy-Weinberg equilibrium. In the first group, patients homozygous for the variant allele T were found to be younger than C allele carriers (39.6 ± 12.5 *vs* 45.7 ± 11.5, $P = 0.008$). Among the histological lesions studied, portal lymphoid aggregates were more frequently observed among TT homozygotes than among C carriers (21/37 *vs* 32/100, $P = 0.008$). The presence of portal lymphoid aggregates was closely correlated with hepatic inflammation ($P = 0.003$) and with bile duct damage ($P < 0.001$). The degree of fibrosis, in contrast, was not found to be related to the *CD14* gene C-159T polymorphism.

CONCLUSION: The data suggest a possible relationship between CD14 C-159T polymorphism and the formation of portal lymphoid aggregates, but not liver fibrosis progression in chronic hepatitis C.

Key words: CD14; Endotoxins; Hepatitis C virus; Inflammation; Lipopolysaccharides; Liver fibrosis; Portal system; Single nucleotide polymorphism

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Askar E, Ramadori G, Mihm S. Endotoxin receptor *CD14* gene variants and histological features in chronic HCV infection. *World J Gastroenterol* 2009; 15(31): 3884-3890 Available from: URL: http://www.wjgnet.com/1007-9327/15/3884.asp DOI: http://dx.doi.org/10.3748/wjg.15.3884

INTRODUCTION

Hepatitis C virus (HCV), which currently infects about 3% of the world's population (an estimated 210 million people), is a major cause of chronic viral liver disease[1]. Chronic hepatitis C is characterized by mostly mild hepatic inflammatory activity which does, however, hold a significant risk of proceeding to liver cirrhosis and hepatocellular carcinoma[2]. Further characteristic histological alterations may include steatosis, bile duct lesions, and portal lymphoid aggregates[3-5]. While steatosis, for instance, has been shown to be associated with HCV subtype infection and is suggested to be modulated by HCV proteins[4,6], progression of fibrosis in chronic hepatitis C has been attributed to age, gender, or alcohol consumption[7], and to host genetic factors[8]. Different genetic backgrounds have also been found to be associated with the susceptibility to HCV subtype infection[9,10].

As a result of its anatomic links to the gut, the liver is constantly exposed to gut-derived bacterial products, e.g. lipopolysaccharides (LPS), which are suggested to be important cofactors in toxin- or ethanol-induced liver disease by exacerbating ongoing injury[11]. Endotoxemia arises from increased translocation of endotoxins from the gut lumen because of altered intestinal permeability and decreased hepatic clearance capacity[12].

Hepatocytes and Kupffer cells, the resident liver macrophages which play a major role in the clearance of systemic bacterial infection, express the membrane-associated form of the endotoxin receptor CD14 (mCD14) at low levels in comparison to peripheral blood monocytes (reviewed by Schwabe *et al*[12]). Moreover, sinusoidal endothelial cells and activated hepatic stellate cells, the main fibrogenic cell type in the injured liver, also express mCD14[12,13]. mCD14 is anchored by glycophosphatidyl inositol, being part of a cell surface receptor complex which additionally contains the dimerized Toll-like receptor 4 and MD-2 (reviewed by Pålsson-McDermott & O'Neill[14]). Furthermore, it also localizes with TLR3, the double-stranded RNA (dsRNA) receptor, in intracellular compartments enhancing dsRNA sensing and TLR3 signalling[15,16]. In addition to the membranous form, a soluble form of CD14 lacking the glycophosphatidyl inositol anchor is thought to modulate LPS responses *via* local stimulatory (promoting) and systemic anti-inflammatory (competing) mechanisms[17].

Recently, a single nucleotide polymorphism (SNP) within the *CD14* gene, rs2569190/C-159T, has been demonstrated to be associated with the risk of developing liver cirrhosis, but not steatosis or less advanced stages of fibrosis, in patients with alcohol-induced liver disease (ALD)[18-20]. These results were attributed to the finding that, *in vitro*, the T allele is more actively transcribed than the C allele[21], leading consequently to the assumption that the TT carriers' hepatic cells may be prone to enhanced inflammatory reactions after endotoxin exposure. The relationship between rs2569190 TT genotype and liver disease progression, however, was not observed in a study by von Hahn and colleagues, in which the variant allele T was alternatively shown to be solely associated with cryptogenic chronic liver disease[22].

The current study aimed to investigate, in two different cohorts, whether the variant position rs2569190/C-159T within the *CD14* gene is associated with hepatitis C liver disease manifestations, and allowed replicated analysis as is demanded for genetic association studies[23].

MATERIALS AND METHODS

Ethics

The study was approved by the local ethical committee and conformed to the ethical guidelines of the 2000 Declaration of Helsinki. Patients gave their informed consent.

Patients

A total of 137 mainly Caucasian chronic hepatitis C patients (mean age 44.0 ± 12.0 years, median 42 years) who consulted the Liver Unit of the Department of Gastroenterology and Endocrinology at the University Medical Center Goettingen (UMG), Germany, between 1993 and 2006 were enrolled. The chronic nature of infection was proven by detection of HCV-specific antibodies and HCV RNA in the patients' sera using a highly sensitive nested reverse transcription polymerase chain reaction (RT-PCR) over a period of at least 6 mo as described[24]. As part of routine clinical evaluation, liver biopsy procedures were performed and liver disease was confirmed in the course of a defined histological evaluation as described below. Biochemical liver disease parameters, i.e. serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (γ-GT) were recorded in parallel. Patients with concomitant non-hepatitis C viral infections and those with continued alcohol or other drug abuse were excluded.

Samples and data from another 349 chronic hepatitis C patients (mean age 45.8 ± 13.5 years, median 45 years) were kindly provided by the German Network of Competence for Hepatitis (Hep-Net)[25].

Determination of HCV genotype

HCV genotyping was performed for the 137 patients (UMG group) using the Innolipa HCV Ⅱ line probe assay (Innogenetics, Ghent, Belgium).

Histological evaluation

Before the start of therapy, liver biopsies were taken from patients for histological evaluation. In brief, sections (5-10 μm) from formalin-fixed and paraffin-embedded liver biopsies were stained with hematoxylin-eosin, trichrome, and Prussian blue. According to Desmet and colleagues, necroinflammatory activity (grading, score 1 to 3), and structural alterations (staging, score 0 to 4) were scored separately[26]. Other lesions typical of hepatitis C such as degree of steatosis (score 0 to 3), the presence or absence of portal lymphoid aggregates, and the presence or absence of bile duct damage were studied additionally as previously described[4]. Hep-Net samples were independently scored by two experienced pathologists according to the German guidelines with regard to inflammation activity and fibrosis progression[25,26].

Isolation of genomic DNA

Genomic DNA (gDNA) was purified from peripheral blood mononuclear cells (PBMCs) using the QIAamp DNA Mini Kit following the blood and body fluid spin protocol (Qiagen, Hilden, Germany). The concentration and the purity of the DNA isolated from PBMCs were determined spectrophotometrically by reading the absorbance levels at 260 and 280 nm. The integrity of gDNA was ascertained through electrophoresis using a 0.6% agarose gel. Alternatively, when PBMCs were not available, gDNA was purified from a 2 mL sample of serum by means of the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions.

SNP genotyping by 5'nuclease assay

gDNA (10 ng derived from PBMCs or an aliquot corresponding to 12.5 μL serum) was amplified in a total volume of 20 μL by real-time PCR using the TaqMan® Universal Master Mix (Applied Biosystems, Darmstadt, Germany) and 36 μmol/L of primers each (CD14: forward 5'-CTAGATGCCCTGCAGAATCCTT-3', reverse 5'-CCCTTCCTTTCCTGGAAATATTGCA-3'). Allelic discrimination was achieved by adding 8 μmol/L differentially fluorescence dye-labeled allele-specific minor

Table 1 Epidemiological characteristics of chronic hepatitis C patients with regard to CD14 rs2569190 genotype (UMG group)

	n	CD14 rs2569190 genotype				MAF	*P*
		CC	CT	TT	*P*		
Total number (%)	137	30 (21.9)	70 (51.1)	37 (27)	0.865[1]	0.526	
Gender (Female/male)	60/77	11/19	36/34	13/24	0.214[2]	0.517/0.532	0.795[3]
Age (mean ± SD)		46.5 ± 13.1	45.3 ± 10.8	39.6 ± 12.5	0.008[a]		
HCV subtype							
1a	31	7 (22.6)	17 (54.8)	7 (22.6)			
1b	73	18 (24.7)	38 (52.0)	17 (23.3)		0.500	
1a + 1b	6	1 (16.7)	3 (50.0)	2 (33.3)			
					0.073[b]		0.087[3]
2a	1	0	0	1 (100.0)			
2b	4	2 (50.0)	1 (25.0)	1 (25.0)		0.630	
3a	22	2 (16.7)	11 (50.0)	9 (33.3)			

MAF: Minor allele frequency. [1]Exact test for the Hardy-Weinberg equilibrium; [2]C carriers *vs* TT (χ^2 test); [3]χ^2 test was applied; [a]C carriers *vs* TT (independent samples *t*-test); [b]C carriers *vs* TT, HCV type 1 *vs* non-type 1 infections (χ^2 test).

groove binder probes (CD14: VIC 5'-CCTGTTACGG TCCCCCTG-3', FAM 5'-CTGTTACGGCCCCCCT-3'). Reactions and analyses were carried out in the sequence detection system ABI prism 7000 (Applied Biosystems, Darmstadt, Germany) according to the supplier's instructions.

Statistical analysis

Quantitative parameters were described by mean and standard deviation or median and inter-quartile range, and the Kolmogorov-Smirnov test was applied to investigate whether these distributions were Gaussian. The UMG group and Hep-Net group were compared regarding age using the parametric independent samples *t*-test.

For describing the ordinal and nominal scaled parameters such as gender, HCV subtype, hepatitis activity, fibrosis, steatosis, portal lymphatic aggregates, and bile duct damage, absolute frequencies and percentages were determined. χ^2 tests were applied to investigate the association of these parameters with the genotype or minor allele frequency (MAF).

To avoid bias, data were also stratified by age (< 44 years, and ⩾ 44 years), and parameters which showed significant correlations to the genotype in the univariate analysis were also analyzed using multivariate logistic regression. The results of stratifying and logistic regression were noted in the text and/or the tables where necessary.

All tests were performed two-sided and the level of significance was set at 0.05. The test results were interpreted in an exploratory way because no alpha adjustment for multiple testing was carried out. Statistical analyses were performed with the assistance of Medistat GmbH, Kiel, Germany, using PASW 17 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Epidemiological characteristics

A total of 137 and 349 patients with chronic hepatitis C (UMG and Hep-Net groups, respectively) were genotyped for the bi-allelic SNP within the *CD14* gene, rs2569190/C-159T. The variant allele T in the first group was found to be about as frequent as the wild-type C allele leading to a CC:CT:TT genotype distribution of 30:70:37 and a T allele frequency of 0.526 (Table 1). Hep-Net patients followed a distribution of 109:170:70 leading to a lower MAF of 0.444 (Table 2). MAFs were close to that given for Caucasians in public databases. The genotype distribution in both groups followed the Hardy-Weinberg equilibrium (Tables 1 and 2, respectively).

No significant difference was found between UMG and Hep-Net patients' regarding gender and age (χ^2 test, $P = 0.781$, independent samples *t*-test, $P = 0.177$, respectively). Epidemiological analysis revealed no significant relationships between the patients' CD14 rs2569190 genotype and gender (Tables 1 and 2). However, when analyzing patients' age with regard to the studied SNP genotypes, the UMG patients homozygous for the variant allele T were found to be on average 6.1 years younger than C carrier patients (mean age, 45.7 ± 11.5 years) at the time of liver biopsy taken before the start of therapy (Table 1). This observation, however, was absent in Hep-Net patients (Table 2).

Similar to the European population, most UMG patients were infected with HCV subtype 1b, followed by 1a and 3a. No significant difference was found between the distribution of HCV type 1 and non-type 1 infections among the three SNP genotypes (Table 1).

Biochemical parameters

Before the start of therapy, AST, ALT, and γ-GT serum activities were recorded for UMG patients as indicators of liver injury in chronic hepatitis C. The median levels of AST and ALT showed an increase from the wild-type to the variant type (Table 3). The number of TT patients with markedly elevated serum ALT activities, i.e. greater than two-fold the upper normal limit, was found to be markedly higher than the number of TT patients with normal ALT activities yielding a slightly increased T allele frequency among patients with markedly elevated ALT (χ^2 test, $P = 0.044$) (Table 3). However, after stratification by age, this was no longer significant (data not shown).

Table 2 Epidemiological characteristics of chronic hepatitis C patients with regard to CD14 rs2569190 genotype (Hep-Net group)

	n	CD14 rs2569190 genotype				MAF	*P*
		CC	CT	TT	*P*		
Total number (%)	349	109 (31.2)	170 (48.7)	70 (20.1)	0.828[1]	0.444	
Gender (Female/male)	148/201	47/62	66/104	35/35	0.151[a]	0.459/0.433	0.484[2]
Age (mean ± SD)		47.2 ± 13.5	44.6 ± 13.6	46.5 ± 13.3	0.616[b]		

[1]Exact test for the Hardy-Weinberg equilibrium; [2]χ^2 test was applied; [a]C carriers *vs* TT (χ^2 test); [b]C carriers *vs* TT (independent samples *t*-test).

Table 3 Biochemical serum parameters and the number of patients with elevated parameters in chronic hepatitis C with regard to CD14 rs2569190 genotype (UMG group)

	CD14 rs2569190 genotype				MAF	[2]*P*
	CC	CT	TT	[2]*P*		
AST (median, IQR)	21.0, 15.8-50.5	28.5, 17.0-52.3	32.0, 16.5-76.5			
[1]Number of patients with elevated/normal AST	9/21	29/41	19/18	0.159[a]	0.588/0.481	0.082
ALT (median, IQR)	36.0, 25.8-85.5	46.5, 26.8-87.3	50.0, 34.5-153.5			
[1]Number of patients with elevated/normal ALT	11/19	38/32	23/14	0.171[a]	0.583/0.462	0.044
γ-GT (median, IQR)	35.5, 13.8-58.8	27.0, 14.0-56.3	32.0, 15.5-53.5			
[1]Number of patients with elevated/normal γ-GT	10/20	19/51	11/26	0.934[a]	0.513/0.531	0.781

AST: Aspartate aminotransferase. Upper normal limit is 19 U/mL for males, and 15 U/mL for females; ALT: Alanine aminotransferase. Upper normal limit is 23 U/mL for males, and 19 U/mL for females; γ-GT: γ-glutamyltransferase. Upper normal limit is 28 U/mL for males, and 18 U/mL for females; IQR: Inter-quartile range. [1]Markedly elevated serum activities of transaminases (> two-fold the upper normal limit) were considered; [2]χ^2 test was applied; [a]C carriers *vs* TT. After stratification by age, all *P*-values were non-significant.

Hepatitis C disease activity and progression

Liver biopsy specimens were taken before the start of an interferon-based therapy and evaluated histologically. Hep-Net patients had higher frequencies of advanced degrees of hepatitis activity and fibrosis progression (Tables 4 and 5) (χ^2 test, $P < 0.001$ for both parameters). Both UMG and Hep-Net patients showed no correlation between their CD14 C-159T genotype and hepatitis activity or fibrosis (Tables 4 and 5, respectively). Other lesions typical and more characteristic of hepatitis C, namely the degree of hepatic steatosis, the presence or absence of lymphoid aggregates and bile duct damage, were additionally studied in UMG patients. With regard to the degree of steatosis and bile duct damage, no significant association with CD14 C-159T genotype distribution could be found (Table 4). T allele homozygous patients, however, were found to have portal lymphoid aggregates more frequently than C carriers (21/37 *vs* 32/100, respectively, χ^2 test, $P = 0.008$) (Table 4).

To avoid spurious findings, a separate analysis was carried out to identify other factors which might underlie the formation of portal lymphoid aggregates. No relationship was found between the presence or absence of portal lymphoid aggregates and sex, age, HCV subtype, biochemical parameters, the stage of fibrosis, or the degree of steatosis (logistic regression analysis, data not shown). In accordance with previous studies, however, a significant relationship between the presence of portal lymphoid aggregates and hepatic inflammatory activity (χ^2 test, $P = 0.003$) and bile duct damage (χ^2 test, $P < 0.001$) was found[3,5,27]. Nevertheless, even in the subgroups which had portal lymphoid aggregates with other lesions, a shift towards the T allele was always observed: 15 TT and 13 CT among the 32 patients who had both a high grade of hepatitis activity and portal lymphoid aggregates: (MAF = 0.672 compared to 0.481 for the remaining patients); 13 TT and 17 CT among the 35 patients who presented with both bile duct damage and portal lymphoid aggregates: (MAF = 0.614 compared to 0.495 for the others) (data not shown).

DISCUSSION

Among chronic hepatitis C patients, no evidence was found for a relationship between the endotoxin receptor CD14 rs2569190/C-159T genotype and the progression of liver fibrosis. This finding was obtained by analyzing two different patient cohorts, one derived from the UMG ($n = 137$) (Table 4), the other from the Hep-Net, a Germany-wide collection of samples ($n = 349$) (Table 5). It is in line with previous findings on Caucasian patients[20,22].

By considering the sum of the evidence, the situation of chronic liver disease resulting from HCV infection appears to be different from the situation of chronic liver disease resulting from alcohol consumption: whereas in ALD, progression of fibrosis was shown to be associated with TT genotypes[18-20], in chronic hepatitis C it did not appear to be related to this genetic variation.

Of note, a recent report found the influence of an environmental factor on the association of rs2569190/C-159T and total serum IgE levels in Russian children[28]. Depending on the *Helicobacter pylori* (*H pylori*) infection status, seronegative or seropositive, the T allele was associated with a decreased or an increased IgE serum concentration, respectively[28]. The observation of the lack of an association of rs2569190/C-159T genotype with chronic hepatitis C disease progression, but an

Table 4 Histological features in chronic hepatitis C-infected patients with regard to CD14 rs2569190 genotype (UMG group) *n* (%)

Histological features	CD14 rs2569190 genotype				MAF	[a]*P*
	CC	CT	TT	[a]*P*		
Hepatitis activity						
Mild	19 (25.0)	40 (52.6)	17 (22.4)		0.487	
Moderate	10 (19.2)	24 (46.2)	18 (34.6)	0.172[b]	0.574	0.152
Severe	1 (11.1)	6 (66.7)	2 (22.2)			
Fibrosis						
Absent	7 (38.9)	6 (33.3)	5 (27.8)		0.517	
Mild	14 (20.6)	35 (51.5)	19 (27.9)			
Moderate	5 (19.2)	15 (57.7)	6 (23.1)	0.758[b]		0.727
Marked	3 (21.4)	7 (50.0)	4 (28.6)		0.539	
Cirrhosis	1 (9.1)	7 (63.6)	3 (27.3)			
Steatosis						
Absent	14 (23.3)	28 (46.7)	18 (30.0)		0.528	
Mild	10 (20.8)	26 (54.2)	12 (25.0)	0.695[b]		0.887
Moderate	5 (26.3)	10 (52.6)	4 (21.1)		0.517	
Marked	1 (10.0)	6 (60.0)	3 (30.0)			
Portal lymphoid aggregates						
Absent	22 (26.2)	46 (54.8)	16 (19.1)	0.008[b]	0.464	0.011
Present	8 (15.1)	24 (45.3)	21 (39.6)		0.623	
Bile duct damage						
Absent	21 (23.6)	46 (51.7)	22 (24.7)	0.411[b]	0.506	0.368
Present	9 (18.8)	24 (50.0)	15 (31.3)		0.563	

[a]χ^2 test was applied to compare mild *vs* moderate and severe hepatitis activity, absent, mild *vs* moderate and marked fibrosis and cirrhosis, and absent, mild *vs* moderate and marked steatosis; [b]C carriers *vs* TT.

Table 5 Hepatitis activity (grading) and fibrosis (staging) in chronic hepatitis C-infected patients with regard to CD14 rs2569190 genotype (Hep-Net group) *n* (%)

	CD14 rs2569190 genotype				MAF	[a]*P*
	CC	CT	TT	[a]*P*		
Hepatitis activity						
Mild	19 (27.1)	35 (50.0)	16 (22.9)		0.479	
Moderate	73 (32.2)	113 (49.8)	41 (18.1)	0.513[b]	0.435	0.359
Severe	17 (32.7)	22 (42.3)	13 (25.0)			
Fibrosis						
Absent	4 (57.1)	2 (28.6)	1 (14.3)		0.449	
Mild	35 (28.9)	61 (50.4)	25 (20.7)			
Moderate	44 (32.8)	63 (47.0)	27 (20.2)	0.928[b]		0.837
Marked	18 (27.7)	37 (56.9)	10 (15.4)		0.441	
Cirrhosis	8 (36.4)	7 (31.8)	7 (31.8)			

[a]χ^2 test was applied to compare mild *vs* moderate and severe hepatitis activity, absent, mild *vs* moderate and marked fibrosis and cirrhosis; [b]C carriers *vs* TT.

association with ALD and the dependency of the association on *H pylori* infection status for an atopy-related parameter, suggests that LPS sensitivity depends on both genetic and environmental factors (gene-environment interaction).

The lack of an association between this CD14 SNP and liver disease progression in chronic hepatitis C patients, is also in accordance with a finding by Huang *et al*[29] who, by functional genomic scanning, identified seven SNPs within seven genes which carry the most relevant risk for developing cirrhosis in Caucasian hepatitis C patients, with CD14 not being among them.

In contrast, a significantly higher frequency of rs2569190 T homozygote hepatitis C patients was found among patients with portal lymphoid aggregates (Table 4). As with lymphocyte infiltrations, primary follicles and secondary follicles in the lymph nodes, portal lymphoid aggregates have been described to occur in various patterns ranging from vague lymphoid aggregation to round defined follicles to well-formed follicles with clearly identifiable germinal centers[30]. Their presence has been attributed to the participation of the host's immune system in liver disease pathogenesis[3,5]. To our knowledge, even today, the etiology and relevance of this manifestation for disease development and/or progression remains unclear. The presence of portal lymphoid aggregates was the only histological manifestation found to be related to CD14 rs2569190/C-159T genotypes (Table 4). As reported in other studies, the presence of portal lymphoid aggregates was found to be closely correlated with bile duct damage and the degree of inflammatory activity[3,5,27], but not with sex, age[3,4], or HCV subtype[4]. The finding of a correlation between portal lymphoid aggregates and HCV subtype 1b infection in Chinese[3] but not European patients is obviously related to a different

HCV subtype distribution. The comparison between subtype 1b- and type 2-infected patients, as is possible among Chinese patients, cannot be carried out among European patients because of the low proportion of type 2 infections. Portal lymphoid aggregates have also usually been found in the early stages of liver disease and to have disappeared in cirrhosis[27,31]. Thus, our finding of a positive association of TT status and the presence of portal lymphoid aggregates, on the one hand, and the absence of an association with disease progression, on the other hand, are concordant with that observation.

The relationship between TT genotype and younger age in the UMG group (Table 1) was neither observed among the patients from the Hep-Net group (Table 2) nor among patients from another German study[20]. In contrast to what might have been expected, these three cohorts do differ in demographic and clinical features. For instance, as outlined, the Hep-Net group comprised a higher proportion of patients with greater degrees of hepatic inflammatory activity and also more advanced stages of fibrosis than the UMG group (Tables 4 and 5). The cohort studied by Meiler *et al*[20] was found to differ significantly in age from the Hep-Net group and both in age and gender distribution from the UMG group (data not shown). Von Hahn's cohort was similar to the UMG and Hep-Net groups with regard to gender distribution, however, further demographic analysis, i.e. association of genotypes and age, was not given[22].

In conclusion, in contrast to what was reported for ALD, our analyses did not reveal an increased risk for chronic hepatitis C patients, homozygous for the CD14 C-159T T allele, to develop more pronounced fibrosis but suggested a relationship of this variation in the formation of portal lymphoid aggregates.

ACKNOWLEDGMENTS

The authors thank all physicians of the Department of Gastroenterology and Endocrinology, UMG, who were involved in the patients' care for their kind cooperation, PD Dr. Stefan Schweyer for his help in histological evaluation of patients' liver biopsies, and Waltraut Kopp for expert technical assistance. Sincere thanks are given to PD Dr. Margarete Odenthal, Institute of Pathology, University of Cologne, for valuable discussions on the manuscript and also to the German Network of Competence for Hepatitis (Hep-Net) for kindly facilitating the use of hepatitis C patients' material and data. Thanks are also given to Ulrike Schulz, Medistat, for professional statistical analyses.

COMMENTS

Background

Progressive hepatic fibrosis develops in patients with chronic liver diseases irrespective of etiology and with a marked inter-individual variability. Different host genetic backgrounds have been shown to act as co-factors in promoting ongoing liver disease progression exacerbated by gut-derived bacterial lipopolysaccharides (endotoxins).

Research frontiers

The variant allele T of a well-known single nucleotide polymorphism (SNP) in the endotoxin receptor *CD14* gene has been reported to be associated with increased alcohol-related liver cirrhosis. In this study, the authors show that the T allele is correlated with the presence of portal lymphoid aggregates rather than being associated with fibrosis progression in chronic hepatitis C virus (HCV) infection.

Innovations and breakthroughs

Recent reports have shown a lack of an association between the T allele and liver fibrosis progression in the context of chronic HCV infection. Genetic association studies, however, require to be replicated. Apart from performing an analysis in two different cohorts, this study is the first to expand the analysis to further histological lesions typical of HCV infection with regard to CD14 rs2569190/C-159T.

Applications

Understanding the mechanisms underlying chronic hepatocellular injury in hepatitis C is important for therapy applications. This study argues for a possible relationship of CD14 rs2569190 T allele in the formation of portal lymphoid aggregates, the presence of which has been attributed to the host's immunological participation in liver disease pathogenesis. Moreover, it excludes a possible role of the variation in promoting fibrosis progression.

Terminology

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen. Cirrhosis is the last stage of fibrosis. A SNP is a variation of one base in the DNA; the nucleotide observed is different from the norm at this position. It occurs with a frequency of > 1% in the normal population. Portal lymphoid aggregates are defined as a densely packed collection of small lymphocytes within the portal tract without or with the formation of a germinal center. Lipopolysaccharide is the main component of the outer cell wall of gram-negative bacteria.

Peer review

This is a valuable population-based association study, which is useful for examining a well-known genetic variation with a role in a common multifactorial disease that may have a strong environmental component. In contrast to the situation in alcoholic liver cirrhosis, the SNP rs2569190/C-159T is not related to chronic HCV-induced fibrosis progression, but to another histological feature, namely, the presence of portal lymphoid aggregates.

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