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Polymorphism in tumor necrosis factor-related apoptosis-inducing ligand receptor 1 is associated with poor viral response to interferon-based hepatitis C virus therapy in HIV/hepatitis C virus-coinfected individuals

Stacey A. Rizza^a, Nathan W. Cummins^a, David N. Rider^b, Sahar Saeed^c, Marina B. Klein^c, and Andrew D. Badley^a

^aDivision of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

^bBiomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

^cDivision of Infectious Diseases, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada

Abstract

Objective(s)—HIV/hepatitis C virus (HCV) coinfection causes accelerated liver disease compared to HCV monoinfection, and only 30–60% of HIV/HCV-coinfected individuals respond to HCV therapy with pegylated interferon and ribavirin. There are currently no biomarkers that predict treatment response in these coinfecting patients.

Design—We investigated whether there is an association between HCV treatment response and SNPs of apoptosis-related genes during HIV/HCV coinfection.

Method—Genomic DNA from 53 HIV/HCV-coinfected individuals was analyzed for 82 SNPs of 10 apoptosis-related genes.

Results—We found that the presence of the rs4242392 SNP in tumor necrosis factor receptor superfamily, member 10a (TNFRSF10A), which encodes for tumor necrosis factor-related apoptosis-inducing ligand receptor 1, predicts poor outcome to HCV therapy, in HIV/HCV-co-infected patients [odds ratio 5.91 (95% confidence interval 1.63–21.38, $P = 0.007$)].

Conclusion—The rs4242392 SNP of the tumor necrosis factor-related apoptosis-inducing ligand receptor 1 gene predicted poor interferon-based HCV treatment response in HIV/HCV-coinfected patients.

Keywords

apoptosis; hepatitis C virus; HIV/hepatitis C virus; polymorphism; tumor necrosis factor-related apoptosis-inducing ligand receptor 1; treatment response

Introduction

Approximately, 30% of HIV-infected patients in developed countries are coinfecting with hepatitis C virus (HCV) due to shared routes of transmission [1]. The negative impact of HIV on the natural history of HCV has been well established: compared with those infected with HCV alone, coinfecting persons experience higher levels of HCV replication and more rapid progression to end-stage liver disease and death [2,3].

The current treatment for chronic HCV infection is a combination of pegylated interferon- α (IFN- α) and ribavirin, with IFN being the backbone of HCV therapy over the past decade. However, a significant proportion of individuals will not respond to anti-HCV therapy. Despite completing treatment, only 50–60% of people with the most common genotype in North America and western Europe, HCV genotype 1, will achieve a sustained viral response after HCV treatment [4]. Results of HCV therapy are even worse among those coinfecting with HIV with overall response rates on average closer to 30% [5,6]. Therefore, many individuals are subjected to the cost, inconvenience, and toxicities of medications without a favorable treatment outcome. Although numerous efforts are focused on identifying useful predictive markers for treatment response, specific reliable biomarkers are still lacking.

Although it remains unknown how pegylated IFN/ribavirin effect antiviral response, recent evidence suggests that they drive the host immune system to induce an apoptotic death of infected hepatocytes [7]. Consistent with this model, HCV viral proteins can prevent apoptosis and thereby create a site of viral persistence [8]. Furthermore, HCV clearance after an acute infection or after therapy is associated with greater serum transaminase levels, suggesting enhanced hepatocyte death [9]. In detailed animal studies, histological examination of the livers of chimpanzees that cleared HCV had greater T cell infiltrates and hepatocyte apoptosis than those that did not respond to treatment and clear the HCV infection [10]. The amount of hepatocyte cell death correlated with serum alanine aminotransferase (ALT) levels, which peaked several days later [10]. Furthermore, previous investigation of predictive markers of HCV treatment has shown that patients who respond to HCV treatment have elevated expression of message for tumor necrosis factor superfamily member 10 (TNFSF10), which encodes the protein tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [11] and elevated serum levels of soluble Fas and soluble Fas-L [12], both of which are involved in the induction of apoptosis.

Host genetic polymorphisms have also been reported to determine the likelihood of HCV treatment response. Genetic analysis of participants in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial found that HCV treatment response in HCV-monoinfected individuals was associated with a SNP in the IL-10 promoter [13]. More recently, polymorphisms in the IL-28B gene were associated with response to pegylated IFN and ribavirin therapy, though it remains unknown what effect these polymorphisms have on protein function [14]. It is unknown what SNPs predict treatment response in HIV/HCV-coinfecting patients. Therefore, we examined whether there was an association between polymorphisms in genes involved in death receptor-mediated apoptosis, including Fas, TRAIL, and TNF, and the response to IFN-based HCV therapy in patients coinfecting with HIV/HCV.

Materials and methods

Study population

The Canadian Co-infection Cohort Study (CCC) is a prospective open cohort of HIV/HCV-coinfecting patients recruited from 16 centers across Canada [15]. Eligible patients are adults

aged 16 years and older with documented HIV infection and with chronic HCV infection or evidence of HCV exposure. The study was approved by the research ethics boards of the participating institutions. With written informed consent from each participant, the study was conducted on blood specimens from 64 individuals from the CCC who received HCV treatment between 2003 and 2009. DNA was only available for 53 patients; therefore, the analysis was performed in those 53 samples. The patients included 12 women and 52 men with a median age of 44 years with a range of 27–62 years. Patient demographics are listed in Table 1. Each patient received IFN-based treatment for at least 12 weeks. A patient was considered a treatment responder if HCV RNA was undetectable at week 12 of treatment and remained so 6 months after treatment was completed.

Genotyping

Sufficient DNA was available on 53 samples. A total of 96 tagSNPs were analyzed in the following genes: BID, CASP10, CASP8, CFLAR, FADD, FAS, MCL1, TNFSF10A, TNFSF10B, and TNFSF10. Fourteen SNPs were removed because of failed genotyping. Therefore, analysis was performed using 82 remaining SNPs (listed in Supplementary Table 1, <http://links.lww.com/QAD/A81>).

SNP selection

To create ld tagSNPs for the 10 candidate genes, we used genotypes from the Hapmap Phase II project (<http://www.hapmap.org>) and two gene resequencing programs: Seattle SNPs (<http://pga.mbt.washington.edu/>) and NIEHS SNPs (<http://egp.gs.washington.edu/>). To determine the Hapmap SNPs for each of the candidate genes, we picked SNPs 5 kb upstream and downstream of each gene. Our gene and SNP coordinates were based on RefSeq release 29 (NCBI build 36) and dbSNP build 129. If the gene had been resequenced in Seattle SNPs or NIEHS SNPs, we used genotypes from those sources as well. At the time we picked these SNPs, NIEHS SNPs had resequenced three of our candidate genes and Seattle SNPs had resequenced none.

To pick ld tagSNPs, we ran ldSelect on each gene for each genotype source (Hapmap, Seattle, NIEHS) for the Caucasian samples in those public sources. We used an r^2 of 0.90 and a minor allele frequency (MAF) cutoff of 0.15. To determine the best source of genotypes for each gene where a gene had been resequenced, we took the source with the higher number of ld bins for the Caucasian samples after bins were removed that did not have a tagSNP with an assay score of 0.4 or greater. If each source (e.g., Hapmap, NIEHS) had the same number of bins, we used Hapmap as the best source because of its higher number of samples (60 unrelated Caucasian samples). Hapmap was chosen as best source for nine genes and NIEHS for one gene.

After the best source was chosen for each gene, the tagSNP with the best chance of success on the Illumina Golden Gate platform was picked as the representative SNP for a bin. We then removed six intronic tagSNPs in singleton bins with the lowest assay score to hit the target of 96 SNPs.

Statistical analysis

Allele frequencies from responders and nonresponders were estimated using observed genotype frequencies. The genotype frequencies in the sample were compared to allele frequencies expected under Hardy–Weinberg equilibrium using a Pearson's goodness-of-fit test or Fisher's exact test ($MAF < 0.05$). Individual SNPs were examined using unconditional logistic regression to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) separately for heterozygotes and minor allele homozygotes, using homozygotes for the major allele as the reference. A P trend was calculated assuming an

ordinal (log-additive) genotypic relationship. We also conducted haplotype analysis using all SNPs from a gene to determine haplotype frequencies, and a global score test was used to determine significance as implemented in the S-plus program *Haplo.stats*.

Results

Genetic polymorphisms and sustained virologic response to hepatitis C virus therapy

The study population included 53 participants for whom genomic DNA was available with HIV/HCV coinfection who received IFN-based therapy. The participants included 11 women and 42 men with a mean age of 44 years. Complete participant demographics and the clinical characteristics of HCV treatment responders versus nonresponders are shown in Table 1. Nonresponders were more likely to be infected with HCV genotype 1, to have higher transaminases, and have more fibrosis (as measured by the APRI), but were similar in other respects to responders.

Eighty-two SNPs in the following death-inducing ligand apoptosis-related genes – BID (BH3 interacting domain death agonist), CASP10 (caspase 10), CASP8 (caspase 8), CFLAR (caspase 8 and FADD-like apoptosis regulator), FADD (Fas-associated via death domain), FAS (Fas), MCL1 (myeloid cell leukemia sequence 1), TNFRSF10A (TNF receptor superfamily member 10A), TNFRSF10B (TNF receptor superfamily member 10B), TNFSF10 [TNF (ligand) superfamily member] – were genotyped in the study participants.

In order to determine an association between genetic polymorphisms and response to HCV therapy, we analyzed the genotype distribution of the 82 SNPs in our patient population. Among the 82 polymorphisms evaluated, only one was associated with response to HCV therapy. We found that those who did not respond to IFN-based HCV therapy were more likely to have the SNP rs4242392, which is contained within an intron in tumor necrosis factor receptor superfamily, member 10a (TNFRSF10A), which encodes for TRAIL receptor 1 (TRAIL R1). Of the patients who did not respond to IFN-based therapy for HCV, 13 out of 34 patients had observed homozygosity for the major allele ‘T’ and one had homozygosity for the minor allele ‘C’ for the rs4242392 SNP. In those who did respond to HCV therapy, 15 out of 19 controls had observed homozygosity of the major allele and none was homozygous for the minor allele. This represents a MAF of 0.32353 for patients and 0.10526 for controls, and an ordinal effects OR of 5.91 (95% CI 1.63–21.38, *P* value 0.007). Analysis of the remaining 81 polymorphisms failed to show an association between genotype and treatment response to HCV therapy.

Fine mapping rs4242392

We assessed SNPs in linkage disequilibrium in the Hapmap Central European ancestry residents of Utah (CEU) population with rs4242392 and did not find any other SNPs in the Hapmap CEU population with a pairwise $r^2 \geq 0.7$. The highest r^2 correlation with our SNP was 0.50 (rs6557628). We then assessed SNPs in linkage disequilibrium with rs4242392 in 60 unrelated CEU samples from the 1000 genomes pilot 1 project and found seven intronic SNPs with a pairwise $r^2 \geq 0.7$ [rs4385477 (1.0), rs73222596 (1.0), rs4872088 (1.0), rs4872089 (1.0), rs73222601 (0.82), rs73222600 (0.77), rs73222599 (0.72)], which would be good candidates for additional genotyping.

Discussion

Human and animal models of HCV infection demonstrate that HCV clearance is associated with greater levels of markers of inflammation, increased hepatocyte apoptosis, and elevated serum levels of transaminases [10]. We, therefore, postulated that alterations in host apoptosis signaling may influence the rate of viral clearance. In addition, the pathogenesis of

HIV is intrinsically linked to altered apoptosis regulation, so we chose to perform this study in HIV/HCV-coinfected patients. Hence, we performed a targeted genetic analysis of polymorphisms within 10 apoptosis-related genes to determine whether they were associated with HCV clearance. Our results demonstrate that the polymorphism rs4242392 in the TNFSF10A gene is associated with nonresponse to IFN-based therapy in our cohort of HIV/HCV-coinfected patients. This gene encodes the TRAIL R1.

TRAIL is an evolutionarily conserved apoptosis-inducing ligand, which induces apoptosis upon binding to its death-inducing receptors TRAIL R1 and/or TRAIL R2 [16]. Knockout studies suggest that TRAIL is involved in immune surveillance against autoimmunity, malignancy, and viral infections. Consistent with such a role, recent evidence indicates that many polymorphisms found within the TRAIL: TRAIL receptor system impact TRAIL signaling [17], and these polymorphisms also impact the incidence of cancer, including breast and colon cancer [18,19], as well as multiple sclerosis [20]. Importantly, polymorphisms within the promoter region of TRAIL have been implicated in the pathogenesis of multiple sclerosis [21] as well, suggesting that both the level of expression and the function of the expressed protein can influence disease penetrance.

Dysregulated TRAIL: TRAIL receptor expression or signaling is increasingly being implicated in the immunopathogenesis of viral infections, including influenza [22], HIV, and HCV (reviewed in [16]). For example, TRAIL has been argued to contribute to the CD4⁺ T-cell depletion during progressive HIV disease [23], has been suggested as a novel therapy to eradicate HIV-infected cells [24], and polymorphisms in TRAIL have been associated with reduced CD4⁺ T-cell gains following antiretroviral therapy [25]. In the case of HCV, patients infected with HCV uniformly have increased expression of the TRAIL on hepatocytes [26].

Interestingly, a major effect of IFN- α treatment is the enhanced expression of TRAIL by effector cells of the immune system, including T cells and natural killer (NK) cells [27] and high level of TRAIL expression by NK cells is associated with therapeutic clearance of HCV [7]. It is possible that IFN-stimulated T cells and NK cells, which express heightened levels of TRAIL, are killing the virally infected TRAIL receptor bearing HCV-positive cells in cases in which IFN treatment results in the cure of HCV. Such a model would predict that any patient in whom IFN treatment causes TRAIL upregulation on effector cells and in whom TRAIL receptor function is preserved, HCV should be cured. Conceivably, the observation that not all patients are cured by IFN might be explained by differences in TRAIL/TRAIL receptor expression and/or function, perhaps as a result of the polymorphic variation.

Although this is a relatively small sample size and not all patients in the study received the same treatment (a few participants received IFN rather than the newer formulation, pegylated IFN, though this was a minority of the population), we believe that the strength of the association and the biologic plausibility of the association suggests a role for TRAIL in determining HCV treatment response. Furthermore, the results are consistent with those reported by Huang *et al.* [11] who analyzed published time series microarray gene expression profiles of patients who did or did not respond to IFN-based HCV therapy. They found 30 differentially expressed genes between 17 Caucasian patients with a good response versus 13 with a poor response; their findings suggest that TNFSF10 played a role in treatment response. Our results expand upon the microarray gene expression data by specifically identifying a polymorphism in the TRAIL R1 gene that is linked to HCV treatment response.

In summary, these results illustrate the potential use of the rs4242392 TNFRSF10A polymorphism as a novel genetic biomarker for poor response to IFN-based HCV therapy. Further validation in separate and larger cohorts is needed before this potential biomarker is ready for widespread clinical application.

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Table 1

Characteristics of interferon treatment responders versus nonresponders.

Characteristics	Responder <i>n</i> =22 (%)	Nonresponders <i>n</i> =31 (%)
Median age (years)	47 (range: 25–65)	44 (range: 25–62)
Sex		
Female	5 (23)	6 (19)
Male	17 (77)	25 (81)
HCV genotype		
1A	7 (32)	13 (42)
1B	2 (9)	4 (13)
2A	1 (5)	0
3A	7 (32)	6 (19)
4	2 (9)	3 (10)
Genotype missing	3 (14)	3 (10)
HCV treatment		
Pegylated interferon/ribavirin	19 (86)	28 (90)
Interferon/ribavirin	1 (5)	2 (6)
Interferon type unspecified	2 (9)	1 (3)
Mean ALT (U/l)	31 (9–133)	59 (18–564)
Mean AST (U/l)	34 (15–89)	62 (19–424)
APRI		
Median APRI score	0.50 (0.17–1.99)	0.90 (0.26–8.30)
APRI >1.5	2 (9)	9 (29)

ALT, alanine aminotransferase; APRI, AST-to-platelet-ratio index; AST, aspartate aminotransferase. APRI > 1.5 has been validated as a marker of significant liver fibrosis (e.g., ≥ F2).