

Interaction of IFNL3 with insulin resistance, steatosis and lipid metabolism in chronic hepatitis C virus infection

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Abstract

Metabolic changes are inextricably linked to chronic hepatitis C (CHC). Recently polymorphisms in the IFNL3 (IL28B) region have been shown to be strongly associated with spontaneous and treatment induced recovery from hepatitis C virus (HCV) infection. Further, circumstantial evidence suggests a link between IFNL3 single nucleotide polymorphisms and lipid metabolism, steatosis and insulin resistance in CHC. The emerging picture suggests that the responder genotypes of IFNL3 polymorphisms are associated with a higher serum lipid profile, and less frequent steatosis and insulin resistance. This review analyzes the current data regarding this interaction and its meaning for HCV pathogenesis and disease progression.

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Key words: IFNL3; Chronic hepatitis C; Insulin resistance; Lipids

Core tip: Metabolic changes are inextricably linked to chronic hepatitis C (CHC). Recently polymorphisms in the IFNL3 region have been shown to be strongly associated with spontaneous and treatment induced recovery from hepatitis C virus (HCV) infection. Further, circumstantial evidence suggests a link between IFNL3 single nucleotide polymorphisms and lipid metabolism, steatosis and insulin resistance in CHC. The emerging picture suggests that the responder genotypes of IFNL3 polymorphisms are associated with a higher serum lipid profile, and less frequent steatosis and insulin resistance. This review analyzes the current data regarding this interaction and its meaning for HCV pathogenesis and disease progression.

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INTRODUCTION

Hepatitis C virus (HCV) infection affects about 170 million people worldwide. It leads to slow but progressive hepatic inflammation and fibrosis in as many as 70% of infected individuals. Over time, 20% will develop cirrhosis and its related complications, and about 1%-2% of subjects may develop hepatocellular carcinoma after 2-3 decades of infection^[1]. The natural history of HCV infection in terms of chronicity and disease progression seems to be largely determined by the host immune response to

virus-infected hepatocytes. The interplay between many viral, host, genetic and environmental factors modifies the course of HCV infection and the degree of hepatic inflammation. In this context, the discovery of the association between IFNL3 polymorphisms and spontaneous or treatment induced clearance of HCV presented a major milestone in the study of chronic hepatitis C (CHC)^[2-5].

Metabolic syndrome is a constellation of problems that includes obesity, dyslipidemia, diabetes, and insulin resistance^[6]. The prevalence of metabolic syndrome is increasing, paralleling the obesity epidemic worldwide and in the United States and European countries especially^[7]. Multiple levels of interaction between HCV, metabolic syndrome and genetics have been recently postulated, including a molecular interaction between IFNL3 polymorphisms and HCV associated glucose and lipid metabolism. In this review we summarize the current clinical evidence for an interaction between IFNL3 polymorphisms and metabolic syndrome, and its clinical implications.

IFNS LAMBDA AND HCV

The type III interferon (IFN) or IFN- λ (IFNL) family consists of three members: IFN- λ 1, IFN- λ 2 and IFN- λ 3 (formerly known as IL-29, IL-28A and IL-28B), which were discovered in 2003 by computational prediction and are genetically distinct from type I IFNs^[8,9], and a fourth, IFN- λ 4, recently described from primary human hepatocytes^[10]. Another recent study identified a novel TT/-G polymorphism in the CpG region upstream of IL28B, which is a better predictor of HCV clearance than rs12979860^[11]. Whereas IFN- α binds to the constitutively expressed type I IFN receptor in almost all nucleated cells, IFN- λ cytokines bind to a heterodimer of part of the IL-10 receptor and the IFNL receptor (IL10RA and IL28R, respectively)^[12], the latter of which is only expressed in restricted cell types, including epithelial cells, plasmacytoid dendritic cells and hepatocytes^[13]. IFNL stimulation results in the upregulation of interferon stimulated genes (ISGs) *via* the Jak-STAT (Janus kinase-signal transducer and activator of transcription) pathway similar to type I IFNs^[12,14].

In an attempt to identify host genetic markers for IFN responsiveness to predict treatment outcome in CHC, genome-wide association studies identified single nucleotide polymorphisms (SNPs) in the IFNL3 (IL28B) region to be strongly associated not only with response to treatment with pegylated IFN- α (Peg-IFN- α) with ribavirin (RBV) in HCV genotype 1 infection^[2-5], but also spontaneous recovery^[15] (Table 1). This association has been validated in different ethnic populations and for various HCV genotypes^[16,17]. In a recent meta-analysis, IFNL3 polymorphisms seem to be clinically useful even in the era of new direct acting antiviral drugs^[18]. Moreover, the responder genotypes of the IFNL3 polymorphisms have been reported to be associated with increased hepatic inflammation in CHC patients^[2,19].

Table 1 Summary of the IFNL3 polymorphisms identified by genome-wide association studies

GWAS	Total population	IFNL3 SNP	Wild (responder) type/non-responder allele
Suppiah <i>et al</i> ^[3]	848	rs8099917 ²	T/G
Tanaka <i>et al</i> ^[4]	314	rs8099917 rs12980275	T/G A/G
Rauch <i>et al</i> ^[5]	914	rs8099917	T/G
Ge <i>et al</i> ^[9]	1137	rs12979860 ¹	C/T

¹rs12979860 and ²rs8099917 single nucleotide polymorphisms (SNPs) are strongly associated with clearance and commonly used in clinical practice. GWAS: Genome-wide association studies.

HCV-ASSOCIATED METABOLIC CHANGES

CHC can be considered not only a viral disease, but also a metabolic disease. HCV interacts with lipid metabolism leading to steatosis, it impairs glucose metabolism leading to insulin resistance (IR) and diabetes mellitus type II and is associated with an increased risk of carotid atherosclerosis^[20,21].

The prevalence of steatosis in patients with CHC is reported to be between 40% and 80% depending on the features of the population studied in terms of alcohol consumption, prevalence of overweight/obesity, diabetes and other risk factors for fatty liver^[22,23]. However, when all common contributing factors to steatosis have been excluded, the prevalence of steatosis in CHC still remains about 40%. This figure represents an approximately 2-fold increase compared to the prevalence of steatosis in other common chronic liver diseases such as chronic hepatitis B virus infection (20%)^[24].

Various studies have shown that both host and viral factors may contribute to the development of steatosis, with the relative importance of each varying with HCV genotype. In particular, in patients infected with HCV genotype 3, steatosis seems to be mostly virus-induced and often severe^[2,25]. In contrast, in patients infected with non-genotype 3, steatosis seems to be mainly associated with host metabolic factors and correlates with body mass index (BMI) and central adiposity^[3,26,27].

Steatosis is known to have deleterious clinical consequences in CHC, as it is associated with accelerated progression of liver fibrosis^[28] and probably HCC^[29]. It has also been shown in large clinical trials that steatosis impairs the response to antiviral therapy^[30]. However, the effect is more prominent in patients with non-3a genotype^[30], likely due to IR as the underlying mechanism affecting the response to standard dual therapy with Peg-IFN- α /RBV, and suggesting that the viral steatosis does not impair response to treatment^[25]. Increasing levels of IR are associated with reduced rates of rapid virological response (RVR) as well as sustained virological response (SVR) in patients with HCV genotype 1, 2, 3 and 4 infections when treated with dual therapy comprising Peg-IFN- α and RBV^[31-33]. This observation has been confirmed in two meta-anal-

yses^[34,35]. A direct correlation between lipid profiles and the virologic response to Peg-IFN- α and RBV was also reported in some recent studies^[36,37].

IFNL3 POLYMORPHISM AND LIPID METABOLISM

Since the discovery of the correlation of IFNL3 polymorphisms with HCV clearance, there is an accumulating body of evidence about an association between these polymorphisms and metabolic changes in CHC.

The IFNL3 responder genotype is associated with less pronounced disturbances of lipid metabolism in CHC, as reflected by higher serum cholesterol and lipoprotein levels: CHC genotype 1 individuals with IFNL3 rs12979860 CC genotype have significantly higher apolipoprotein B and low-density lipoprotein cholesterol (LDL-C) levels^[38], and lower serum apolipoprotein E levels^[39], compared to those with the non-responder CT and TT genotypes. In accordance with these findings, another study from Japan showed that the responder genotype of rs8099917 TT was associated with high LDL-C levels and high SVR^[40]. This association may result from suppression of hepatic lipase and lipoprotein lipase by endogenous interferon, which in turn decreases serum LDL-C, implying a stronger endogenous interferon response to HCV in those subjects^[36].

In a small cohort (55 patients), Sheridan *et al.*^[39] showed that although HCV RNA was significantly higher in those with rs12979860 CC genotype, this difference was mainly accounted for by a higher non-lipoprotein particles (LVP) fraction. It is known that LVPs are low-density HCV particles that have high infectivity^[41]. This may partially explain the paradox that the IFNL3 responder genotypes have higher HCV RNA total viral load, despite high viral load being a negative predictor of SVR^[42]. However, further confirmation of this data in larger cohorts is required before any final conclusion can be extracted.

Chiba-Falek *et al.*^[43] investigated the genetic basis for the variance of LDL-C and apolipoprotein B levels in CHC patients and their potential interaction with IFNL3 genotype: Their data show that two of the APOE genomic region polymorphisms, rs7412 and rs429358 (which defines the ϵ 4 isoform), appear to be associated with serum lipoprotein levels in HCV patients. Polymorphisms in ϵ 4, however, were not associated with apolipoprotein E levels in HCV-infected Caucasians patients (in contrast to a healthy control cohort), and the overall amount of variance in serum apolipoprotein E levels explained by APOE genotype was much lower in the HCV cohort (7% *vs* 20%). A recent genome-wide association studies in non-HCV-infected cohorts suggested associations of polymorphisms at the TOMM40-APOE genomic region with multiple lipid traits (LDL-C, triglycerides)^[44]. In particular, two nonsynonymous SNPs in exon 4 of the APOE gene, rs429358 and rs7412 have been associated with lipid levels^[44]. Further this study also refers

to a potential interaction between TOMM40-APOE and IFNL3 polymorphisms, as rs429358 was associated with apolipoprotein B levels in a IFNL3 genotype dependent manner, *i.e.*, the effect was more profound in patients carrying rs12979860 CC, than those carrying rs12979860 CT/TT. These results together suggest that HCV-associated dyslipidemia may not be controlled to the same extent by the same genes that affect lipids/lipoproteins in healthy (non-HCV infected) cohorts^[43].

There is increasing evidence that the life cycle of HCV is directly linked to host lipoproteins: (1) HCV circulates in plasma with lipoprotein as an infectious complex; (2) Hepatocyte lipoprotein receptors are involved in HCV entry; (3) Replication of HCV RNA in hepatic cells is inhibited by inhibitors of lipid metabolism; (4) HCV particles released from hepatocytes are attached to lipoproteins; and (5) Serum lipid profiles (LDL-C, HDL-C and triglycerides) are associated with higher rates of spontaneous or treatment-induced HCV clearance^[45]. At least, the latter is also affected by IFNL3 polymorphisms, opening up the possibility of interaction in mediating this effect. Thus, better understanding of the interaction between lipids, IFNL3 polymorphisms and the HCV life cycle will improve our understanding of HCV pathogenesis and open new avenues in treating HCV infection.

IFNL3 POLYMORPHISM AND STEATOSIS

The relationship between steatosis and IFNL3 genotype is still subject to debate, as the current literature demonstrates conflicting results (see Table 2). A retrospective analysis of 1604 patients enrolled in the IDEAL trial (Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy) of HCV genotype 1 patients showed that the IFNL3 rs12979860 CC responder genotype was significantly associated with higher pretreatment LDL-C levels and less frequent hepatic steatosis^[46]. In keeping with this, other recent studies show the same association between the IFNL3 rs12979860 CC genotype and less frequent steatosis in CHC genotype 1^[47-49]. This observation also extends to two other IFNL3 polymorphisms, rs8099917^[50] and rs12980275, which were associated with steatosis in genotypes non-3^[51]. In contrast, a study from Japan failed to find a significant association between rs8099917 and hepatic steatosis in 122 Japanese Mongolian patients infected with HCV genotype 1b^[52], and another study from Spain failed to confirm an association between rs12979860 and steatosis in 445 Caucasian patients^[53]. These conflicting results may be owing to the relatively small sample size of these cohorts, differences in ethnicity, population characteristics and local other risk factors for steatosis, different IFNL3 SNPs being investigated, which may exhibit different features, and the respective assessments of individual pathologists.

In the setting of liver transplantation for CHC, a recent abstract presented at the European Association for the Study of the Liver (EASL) meeting 2013 suggested

Table 2 *IFNL3* polymorphisms and steatosis in chronic hepatitis C

No. of patients	Study design	HCV genotype	<i>IFNL3</i> SNP	Results	Ethnicity	Ref.
1604	Retrospective	HCV-1	<i>rs12979860</i>	CC genotype associated with higher pretreatment LDL-C levels and less frequent hepatic steatosis	Caucasians	46
145 180	Retrospective analysis of two Independent cohorts: (1) (antifibrotic) Study cohort; (2) Duke cohort	HCV-1	<i>rs12979860</i>	CC genotype associated with less hepatic steatosis	122 (84.1%) Caucasians 130 (72.2%) Caucasians	47
434	multi-center, Retrospective	HCV-1	<i>rs12979860</i>	CC genotype associated with less frequent hepatic steatosis	Caucasians	48
202	Prospective	HCV-1: 181 (89.6%) HCV-4: 21 (10.4%)	<i>rs12979860</i>	CC genotype associated with less frequent hepatic steatosis	Caucasians	49
153	Retrospective	HCV-1b	<i>rs8099917</i>	TT genotype associated with less hepatic steatosis (vesicular and clear cell changes)	Japanese	50
626	Retrospective analysis of the Swiss Hepatitis C Cohort Study	Non-HCV-3	<i>rs12980275</i>	G associated with less hepatic steatosis only in non-HCV-3	Caucasians	51
122	Retrospective	HCV-1b	<i>rs8099917</i>	No association with hepatic steatosis	Japanese Mongolian	52
445	Retrospective	HCV-1: 303 (68.1%) HCV-2: 13 (2.9%) HCV-3: 82 (18.4%) HCV-4: 47 (10.6%)	<i>rs12979860</i>	No association with hepatic steatosis	Caucasian	53

HCV: Hepatitis C virus; LDL-C: Low-density lipoprotein cholesterol.

Table 3 *IFNL3* polymorphisms and insulin resistance in chronic hepatitis C

Cohorts size	Study design	HCV genotype	<i>IFNL3</i> SNP	% IR	HOMA-IR	Results	Ethnicity	Ref.
434	Multi-center, retrospective	HCV-1 (n = 434)	<i>rs12979860</i>	50%	> 3	CC genotype associated with reduced IR	Caucasians	48
202	Prospective	HCV-1 (n = 181) HCV-4 (n = 21)	<i>rs12979860</i>	32.20% (65/202)	≥ 3	CC genotype associated with reduced IR	Caucasians	49
328	Retrospective	HCV-1 (n = 328)	<i>rs8099917</i>	50% (84/168) in TT genotype vs 69.7% (53/76) in TG/GG genotype	≥ 2.45 in TT genotype vs ≥ 1.55 in TG/GG genotype	No differences in <i>IFNL3</i> genotype distribution according to HOMA-IR	Japanese	57
240	Retrospective	HCV-1 (n = 188) HCV-2 (n = 3) HCV- (n = 30) HCV-4 (n = 19)	<i>rs12979860</i>	46% (89/193)	≥ 2	No differences in HOMA-IR levels according to <i>IFNL3</i> genotypes	Caucasians	59

HCV: Hepatitis C virus; IR: Insulin resistance.

that *IFNL3* rs12979860 TT nonresponder genotypes had an increased incidence of graft steatosis over time, while recipient *IFNL3* was not associated with steatosis^[54].

In an attempt to better understand the interaction of *IFNL3* polymorphisms with other polymorphisms in influencing steatosis, a recent study investigated the interaction between *IFNL3* rs12979860 and the Patatin like phospholipase domain-containing 3 (PNPLA3) rs738409 polymorphism, a strong determinant of hepatic fat accumulation and steatohepatitis^[55]. Albeit, the association between rs12979860 genotype and steatosis was independent of PNPLA3 GG genotype, the rs12979860 CC genotype protected from steatosis only in patients positive for the PNPLA3 G variant, a genetic risk factor for severe steatosis^[56]. In another study, the PNPLA3 G variant showed a close association with steatosis in patients with

rs12979860 CT/TT, but not rs12979860 CC genotype^[53]. These findings suggest a potential interaction between *IFNL3* and PNPLA3 polymorphisms on the risk for steatosis in non-genotype 3 CHC patients, though further analysis is required to better understand the nature of this interaction.

Finally, an interaction between *IFNL3* genotype and an amino acid substitution at residue 70 (aa70) of the HCV core region has been suggested^[52]. Although these authors failed to find a direct association between rs8099917 and hepatic steatosis, they found significant associations between rs8099917 and aa70 and between aa70 and hepatic steatosis^[52]. This suggests that the amino acid at residue 70 of the HCV core region should be considered as a parameter for adjustment in any future studies of the correlation between *IFNL3* genotype and steatosis.

IFNL3 POLYMORPHISM AND INSULIN RESISTANCE

The relationship between IR measured by HOMA and IFNL3 genotype is still subject to debate (see Table 3). Two recent reports showed that the responder IFNL3 rs12979860 CC genotype was associated with reduced IR in HCV genotype 1 patients^[48,49], while other reports failed to find this association^[57-59] with either rs8099917^[57] or rs12979860^[57-59]. Interestingly, a recent study from Spain shows that IR can predict SVR in CHC patients independently of the IFNL3 rs12979860 polymorphism^[59]. This is quite intriguing as it sheds new light on the clinical observations linking higher LDL, less steatosis and lower insulin resistance with SVR.

CONCLUSION

In conclusion, the discovery of IFNL3 polymorphisms and their impact on CHC presents a major breakthrough in HCV research. The association of IFNL3 responder genotypes with higher LDL, less steatosis, less insulin resistance and SVR suggests a mechanistic link between IFNL3 and the metabolic syndrome in CHC. This sheds new light on the pathogenesis of CHC and opens exciting avenues to explore. Further work is needed to better understand the mechanistic explanation of these inter-related associations, and its potential implications in improving the current management of CHC patients.

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