Polymorphism Near the Interleukin-28B Gene and Anti-Hepatitis C Viral Response

Yasuhiro Asahina¹,², Mina Nakagawa¹, Sei Kakinuma¹,² and Mamoru Watanabe³

¹Department of Gastroenterology and Hepatology; ²Department of Liver Disease Control, Tokyo Medical and Dental University, Yushima, Bunkyo-ku, Tokyo, Japan

Abstract

In a recent genome-wide association study, single nucleotide polymorphisms (SNPs) located near the interleukin-28B gene (IL28B), which encodes type III interferon (IFN) λ3, were shown to be strongly associated with a viral response to pegylated IFNα (PEG-IFNα) and ribavirin (RBV) combination therapy and spontaneous viral clearance in patients chronically and acutely infected with hepatitis C virus (HCV), respectively. The global distribution of allele frequencies shows a remarkable pattern, in which a favorable allele is nearly fixed in East Asia, has an intermediate frequency in Europe, and is least frequent in Africa. Although the underlying mechanisms responsible for viral responses associated with IL28B SNPs have not been completely elucidated, IFN-stimulated gene expression in patients with unfavorable IL28B genotypes tends to be high at baseline and is insufficiently induced by exogenous IFN administration, resulting in poor treatment outcomes. Clinically, triple therapy with PEG-IFNs/RBV together with direct-acting antiviral agents (DAAs) is currently used to treat chronic hepatitis C as a first-line therapy. Although the predictive power of IL28B status may be attenuated, the IL28B genotype will remain relevant to the outcomes of DAA therapy when used in combination with PEG-IFNα as a backbone. Even with the introduction of IFN-free therapies with a new class of highly effective DAAs, IL28B SNPs are still useful predictors of treatment outcomes and can be used to individualize treatment strategies to maximize cost-effectiveness and identify patients at risk of being refractory to treatment. This review summarizes the current understanding of the clinical significance and role of IL28B in HCV infection and response to therapy.

Keywords: IL28B; IFN; Innate immunity; Interferon-stimulated gene. Abbreviations: HCV, hepatitis C virus; IFN, interferon; PEG-IFNs, pegylated interferons; RBV, ribavirin; DAA, direct-acting antiviral agent; NVR, nonviral response; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; IL, interleukin; SVR, sustained viral response; Jak–STAT, Janus kinase–signal transducer and activator of transcription; ISG, interferon-stimulated gene; RIG-I, retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated gene 5; TLR, toll-like receptor; IPS-1, interferon β promoter stimulator 1.

Introduction

Hepatitis C virus (HCV) infection is a global epidemic, with 130–170 million people currently affected worldwide. It is a common cause of chronic hepatitis, which can progress to liver cirrhosis and hepatocellular carcinoma in many patients. During the last two decades, interferon (IFN)-based therapy has been used to treat chronic hepatitis C with the goal of altering the natural history of this disease. HCV eradication with IFN-based therapy has been shown to prevent hepatocellular carcinoma,⁴,⁵ and triple therapy with pegylated IFNα (PEG-IFNα) and ribavirin (RBV) together with direct-acting antiviral agents (DAAs) is currently used to treat chronic hepatitis C as a first-line therapy. Even with this newest standard of treatment that incorporates DAAs, a response to PEG-IFNα/RBV remains essential to obtain an adequate outcome; non-responders (defined as failure to clear HCV RNA from serum 24 weeks after initiating therapy) and particularly null responders (defined as failure to decrease HCV RNA by <2 logs at 24 weeks after initiating therapy) to PEG-IFNα/RBV also poorly respond to triple therapy that incorporates DAAs. Therefore, determining predictive factors and understanding the mechanisms responsible for responses to PEG-IFNα/RBV remain important for making treatment strategy decisions for individual patients.

In a recent genome-wide association study (GWAS), single nucleotide polymorphisms (SNPs) located near the interleukin-28B gene (IL28B), which encodes type III IFNλ3, were shown to be strongly associated with a virological response to PEG-IFNs/RBV combination therapy.⁶–⁷ Patients infected with HCV genotype 1 who had favorable IL28B genotypes (rs12979860 CC or rs8099917 TT) had significantly better responses to PEG-IFNs/RBV associated with spontaneous clearance of acute HCV infection was more likely in patients with favorable IL28B genotypes.⁸ In contrast, the rs12979860 CT and TT or rs8099917 TG and GG genotypes (unfavorable IL28B genotypes) were strongly associated with a non-viral response (NVR) (defined as patients with detectable HCV RNA during and after treatment) to PEG-IFNs/RBV.⁹ However, the mechanisms involved in resistance to PEG-IFNα/RBV associated with unfavorable IL28B genotypes have not been completely elucidated.

Clinical significance of IL28B SNPs

Marked differences in HCV clearance and response to treatment among ethnic groups have long suggested a role for host genetic factors. A recent GWAS approach used high-throughput
genotyping ranging from 300,000 to 1,000,000 SNPs for each sample. This approach could detect factors strongly associated with disease susceptibility and drug responses without any a priori hypotheses with regard to causative SNPs. Four independent GWASs also assessed genetic variations with regard to the responses to PEG-IFNα/RBV combination therapy for patients with chronic hepatitis C (Table 1). 4–7 In all these studies, the conclusive findings were that SNPs in or near the IL28B gene were strong pretreatment predictors of a sustained virological response (SVR) and NVR. These studies identified two SNPs near the IL28B gene (rs12979860 C/T and rs8099917 T/G). Patients homozygous for the major allele with a so-called favorable genotype (rs12979860 CC or rs8099917 TT) were twice as likely to achieve an SVR compared with patients with a minor risk allele (rs12979860 TT or CT or rs8099917 GG or TG) after PEG-IFNα/RBV combination therapy. The IL28B genotype was also strongly associated with spontaneous clearance of HCV infection. In acute HCV infection, patients who were homozygous for the major allele were more likely to spontaneously clear the virus than those with the minor allele. 8 Among patients with a minor risk allele, the differences in SVR and spontaneous clearance rates were less notable (less than twice) between heterozygotes (rs19979860 CT or rs8099917 TG) and homozygotes (rs19979860 TT or rs8099917 GG).

With regard to the IL28B genotype, the differences in treatment responses to PEG-IFNα/RBV therapy are remarkable in patients with HCV genotype 1. The IL28B SNP is also associated with an SVR in patients infected with the non-1 HCV genotype. 9–11 However, this association is less notable, particularly in patients with genotype 2/3 with rapid virological responses (defined as HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay) 9 and patients with genotype 2a. 10 The allele frequency varies markedly across ethnic groups. Accordingly, differences among population groups were noted in SVR rates in patients treated with PEG-IFNα/RBV and spontaneous HCV clearance. The global distribution of allele frequencies shows a remarkable pattern, in which a favorable allele (C in rs12979860 and T in rs8099917) that results in a greater therapeutic response and natural HCV clearances nearly fixed throughout East Asia, has an intermediate frequency in Europe, and is least frequent in Africa. 8 HCV clearance occurs in 36.4% of individuals of non-African ancestry infected with HCV but in only 9.3% of individuals of African ancestry infected with HCV, which may be explained, in part, by the observed differences in allelic frequency in these ethnic groups.

Both SNPs at rs12979860 and rs8099917 are in strong linkage disequilibrium, but the rs8099917 allele frequency differs among population groups worldwide; thus, its predictive power may vary between diverse cohorts. 14 Because of the significant effect of rs12979860 on treatment outcome, determining this SNP may be sufficient for predicting an SVR in patients infected with HCV genotype 1 who are treated with PEG-IFNα/RBV combination therapy. 15,16 However, haplotypes that include both SNPs may be more accurate than either SNP alone. Although the predictive value for the treatment outcome could not be improved in patients with the rs12979860 CC genotype (homozygous carrier for the responder allele) by also determining the rs8099917 SNP, there was evidence that a significant proportion of heterozygous carriers of the rs12979860 T non-responder allele could profit with respect to SVR prediction by also determining the rs8099917 SNP. 15,16

Pretreatment factors associated with IL28B genotypes

An unfavorable IL28B genotype is associated with several host and viral factors, most of which are unfavorable factors for the response to PEG-IFNα/RBV therapy. However, the mechanisms responsible for the coexistence of these unfavorable factors are currently unknown. Patients with unfavorable IL28B genotypes have significantly higher γ-glutamyltransferase levels, 17 lower low-density lipoprotein cholesterol levels, 18,19 a higher frequency of hepatic steatosis, 20 glutamine or histidine mutations at amino acid position 70 in the HCV core region, 21 and one or no mutations in the IFN sensitivity-determining region in the HCV non-structural 5A gene. 21

Liver fibrosis and IL28B genotypes

An association between the IL28B genotype and risk of liver fibrosis progression remains controversial. A recent cross-sectional study analyzed 1329 patients with HCV genotype 1 and found no relationship between IL28B SNPs and advanced fibrosis. 22 Similarly, Marabita et al. estimated the fibrosis progression rate in 247 patients with known dates of infection and showed that the IL28B genotype had no effect on the risk of developing advanced fibrosis. 23 A recent cohort study revealed a significant relationship between an unfavorable IL28B genotype and a slow fibrosis progression rate; however, this relationship was found only in patients infected with a genotype other than genotype 1, and not in genotype 1-infected patients. 24 Taken together, SNPs near the IL28B gene do not appear to be closely associated with liver fibrogenesis in HCV genotype 1-monoinfected patients. 25

Table 1. Four GWASs identifying SNPs associated with PEG-IFN/RBV therapy

| Ge et al. 4 | Suppiah et al. 5 | Tanaka et al. 6 | Rauch et al. 7 |
|-----------------|-----------------|-----------------|-----------------|
| **Year** | 2009 | 2009 | 2009 | 2010 |
| **Ancestry** | Caucasian/African/Hispanic | Caucasian | Japanese | Caucasian |
| **Number of patients** | 1137 | 293 | 142 | 465 |
| **SNP** | rs12979860 | rs8099917 | rs8099917 | rs8099917 |
| **Odds ratio** | 3.1 | 1.98 | 12.1 | 5.20 |
| **p value** | 1.21 × 10⁻²⁸ | 7.06 × 10⁻⁸ | 3.11 × 10⁻¹⁵ | 5.47 × 10⁻⁸ |
| **HCV genotype** | 1 | 1 | 1 | 1, 2, 3, 4 |
IL28B (IFN-3)

The IL28B gene, also known as the IFN-3 gene, is a member of a highly homologous type III IFN family consisting of three members: IL29 (IFN-I), IL28A (IFN-2), and IL28B (IFN-3). All of these are located on chromosome 19.27-28 The amino acid sequences of IL28A and IL28B have 96% homology, and both are 81% identical to the amino acid sequence of IL29.28 Similar to IFNα, IFNβs are triggered by viral infections and induce antiviral activity through both the innate and adaptive immune systems.29,30

Compared with type I IFN, IFNβs are produced by relatively restricted cell types, including hepatocytes, intestinal epithelial cells, and dendritic cells (including BDCA3+) cells.31 In addition, the type III IFN receptor, a heterodimer of the IL10 and IL28 receptors, is expressed in relatively restricted cell types, including hepatocytes, intestinal epithelial cells, and plasmacytoid dendritic cells.32 Both type I IFN and IFNβs activate the Janus kinase–signal transducer and activator of transcription (Jak–STAT) pathway27,33 after binding to type I and type III receptors, respectively, and induce a significant number of IFN-stimulated genes (ISGs).34 Although both types of IFN induce an overlapping set of ISGs, substantial differences have been observed between type I IFN and IFNβs in terms of the gene expression induced by them.35

The kinetics of ISG induction also differs between IFNα and IFNβs. The initial change in ISG expression in response to IFNα is weaker; however, it gradually increases and is subsequently maintained.34 In contrast, the kinetics of ISGs in response to IFNβ shows a steep peak after induction, as reflected by an earlier stronger induction, which is then followed by a rapid decline.36 Because of these differences between type I and III IFNs, IFNβs may play roles in antiviral activity that are distinct from type I IFNs.

The relationship between IL28B genotypes and basal levels of IL28 expression remains controversial. However, IL28B promoter activity is reportedly lower with unfavorable IL28B SNPs.41,42 In ex vivo induction of IL28B transcripts by poly I:C stimulation is lower in peripheral blood mononuclear cells derived from patients with chronic hepatitis C with unfavorable IL28B genotypes.38 Moreover, BDCA3+ dendritic cells produce larger amounts of IFNβs upon HCV stimulation in patients with favorable IL28B genotypes.31 suggesting that the activity of IFNβ induction may affect treatment outcomes associated with IL28B genotypes.

IFNβ induces intracellular responses similar to those of IFNα but in fewer cell types because of differences in the receptor distribution pattern. This could potentially result in an improved safety profile. In phase I proof-of-concept studies of PEG-IFNα-1, with or without RBV in patients with chronic HCV genotype 1 infections, PEG-IFNα-1 showed an improved safety profile with minimal flu-like symptoms and no significant hematologic changes other than RBV-associated decreases in hemoglobin compared with PEG-IFNα.39

Innate immunity and IL28B genotypes: proposed role for IL28B in response to IFN

The innate immune system plays an essential role in host antiviral defense against HCV infection.40 The retinoic acid-inducible gene I (RIG-I), a cytoplasmic RNA helicase, related melanoma differentiation-associated gene 5 (MDA5), and toll-like receptor 3 (TLR3) play essential roles in initiating the host antiviral response by detecting intracellular viral RNA41,42 (Fig. 1). The IFNβ promoter stimulator 1 (IPS-1), also called the caspase-recruiting domain adaptor inducing IFNβ, mitochondrial antiviral signaling protein, or virus-induced signaling adaptor, is an adaptor molecule. IPS-1 connects RIG-I sensing to downstream signaling, resulting in IFNβ and IFNα gene activation.43-46

IFNβ binds to the type I IFN receptor, whereas IFNα binds to the type III IFN receptor comprising an IL10R–IL28R receptor complex.47 Both the receptors activate the Jak–STAT pathway, which upregulates a large number of ISGs by activating the IFN-stimulated response element.47 In recent reports, IFNα and not type I IFN was shown to be primarily induced by HCV infection, which subsequently enhanced ISG expression in primary human hepatocytes.48 The degree of hepatic IFNα induction was closely correlated with the strength of the ISG response.49 Thus, hepatic IFNβs may be essential for inducing ISGs and subsequent HCV eradication.

Considerable attention has been paid to the relationships between ISG induction, IL28B genotypes, and treatment outcomes. Several reports, including ours, have demonstrated that intrahepatic gene expression levels of ISGs and levels of cytoplasmic viral sensors such as RIG-I and MDA5 (known as RIG-I like receptors) were markedly upregulated at baseline and were poorly induced by exogenous IFNα administration in NVR when treated with PEG-IFNα/RBV combination therapy.50,51 Similarly, hepatic expression of ISGs and RIG-I-like receptors in patients with unfavorable IL28B genotypes was significantly upregulated compared with that in patients with favorable IL28B genotypes.52-54

However, even in a subgroup with unfavorable IL28B genotypes, ISG and RIG-I expression was significantly higher in NVRs than in virological responders.52 Similar tendencies were observed in a subgroup with favorable IL28B genotypes, in which ISG and RIG-I expression was higher in NVRs than in virological responders.52 Therefore, ISG and RIG-I expression is likely to be the best predictor of treatment response regardless of the IL28B genotype, and higher expression of these genes may be a more fundamental phenomenon for IFN resistance.51,52

ISG upregulation by endogenous IFN in the presence of intracellular HCV and the poor response of ISGs to exogenous IFN are closely associated with essential mechanisms. An unfavorable IL28B SNP results in the continuous activation of a subset of ISGs in the presence of intracellular HCV.52 However, this level of expression is insufficient to eliminate HCV from infected cells because it may upregulate IFN-inhibitory molecules such as the suppressor of cytokine signaling 3 (SOCS3) and the protein inhibitor of activated STAT (PIAS), thereby reducing sensitivity to IFN signaling.55 Therefore, infected cells are not only unable to clear the virus but are also unable to promote stronger ISG induction when IFN is exogenously administered during therapy.50

Recently, IFN-α4, a new IFN gene, was discovered by RNA sequencing using primary human hepatocytes that were activated with synthetic double-stranded RNA to mimic HCV infection.56 The IFN-α4 protein has 179 amino acids and is a frameshift variant that is created by ss469415590 (ΔG); a dinucleotide variant, ss469415590 (TT or ΔG), is in high linkage disequilibrium with rs12979860. IFN-α4 induces STAT1 and STAT2 phosphorylation and upregulates ISGs by activating the IFN-stimulated response element. However, this preactivation of IFN signaling induced by IFN-α4 impairs HCV clearance and prevents further activation by exogenous
type I and type III IFNs, which is required for efficient HCV clearance (Fig. 1). Although the mechanisms responsible for this impairment are unclear, the innate immune response in patients with unfavorable IL28B SNPs may have adapted to a different equilibrium state compared with that in patients with favorable IL28B SNPs.

**IL28B SNPs and triple therapy with DAAs**

The IL28B genotype status is one of the most important pretreatment predictors of response to PEG-IFNα/RBV therapy. The treatment regimen for chronic HCV has changed dramatically with the development of DAAs, which directly inhibit specific HCV or host molecules required during the steps of the HCV lifecycle, including HCV NS3-4A protease, NS5B polymerase, and NS5A phosphoprotein, as well as host cell proteins involved in HCV replication.57 Because the predictive role of IL28B SNPs is based on PEG-IFNα/RBV combination therapy, the key question is whether the IL28B genotype will remain a useful predictor of treatment outcomes for triple therapy with DAAs.

A recent report revealed that the SVR rate with triple therapy with telaprevir/PEG-IFNα/RBV was high (84%) for patients with a favorable IL28B genotype, irrespective of any substitution in HCV core aa70. In patients with unfavorable IL28B genotypes, those with HCV core aa70 wild-type achieved a high SVR rate (50%), whereas those with HCV core aa70 mutant achieved an SVR rate of only 12%. This suggests that genetic variations near the IL28B gene and an HCV core amino acid substitution are predictors of SVR to triple therapy for patients infected with HCV genotype 1b.58 However, for patients enrolled in the PILLAR study, a phase IIb study of simeprevir (TMC435; a second-generation NS3-4A protease inhibitor) in combination with PEG-IFNα2b/RBV for treatment-naïve HCV genotype 1 patients, high rates of viral response were achieved for all patients regardless of the IL28B genotype.

Therefore, the predictive power of IL28B status may be attenuated in the setting of triple therapy with more potent DAAs.58,59 However, the IL28B genotype will remain relevant to the outcomes of DAA therapy when used in combination with PEG-IFNα as a backbone. Because an unfavorable IL28B SNP is refractory to a response to IFN signaling and results in failure to suppress the emergence of resistant HCV mutants, IL28B genotyping could be helpful in identifying patients who are poor candidates for triple therapy.

**IL28B SNP and IFN-free DAA combination therapy**

With the development of more potent DAA combinations, IFN-free therapy is likely to be approved in the near future. This raises the question of whether IL28B genotyping will remain a useful predictor of treatment responses. Interim results from a large study designed to evaluate the combination of BI-201335 (NS3-4A protease inhibitor) and BI207127 (non-nucleoside polymerase inhibitor) with or without RBV in chronic hepatitis C patients demonstrated a clear difference in SVR between favorable and unfavorable IL28B genotypes in HCV-1a patients.60 In that study, IL28B, HCV genotype, sex, and pretreatment c-glutamyltranspeptidase levels were identified as factors independently associated with SVR by multivariate analysis. Because the low SVR rates...
observed for HCV-1a patients with unfavorable IL28B genotypes resulted from virological breakthrough in most patients, the IL28B status influenced the emergence of resistant mutant HCVs with IFN-free therapy.

However, this effect of the IL28B genotype was not observed in patients infected with HCV-1b, which is more susceptible to DAAAs than HCV-1a. Moreover, there is also increasing evidence that combination therapy with more potent DAA regimens may reduce the importance of the IL28B genotype as a predictor of treatment response. A recent study of the combination of sofosbuvir (nucleoside polymerase inhibitor) with an NSSA inhibitor (daclatasvir or GS-5885) reported an SVR12 (defined as HCV RNA negative 12 weeks after cessation of treatment) of 100% for HCV-1 treatment-naive patients and prior null responders with unfavorable IL28B genotypes.61,62 Another recent study of the combination of ABT-450/r (NS3-4A protease inhibitor/ritonavir), ABT-267 (NS5A inhibitor), ABT-333 (polymerase inhibitor), and RBV reported an SVR12 of 95% for patients with HCV-1 who were null responders to prior treatment.63

Although the association between IL28B genotypes and treatment outcomes has been attenuated by the development of IFN-free therapy with more potent DAAAs, IL28B genotyping may continue to be useful for identifying patients who should be treated with these potent but expensive regimens as first-line therapy or those who can be treated with shorter or less-expensive regimens.

Conclusions

SNPs upstream of the IL28B gene are associated with spontaneous HCV clearance and response to PEG-IFNα/RBV combination therapy. Although the underlying mechanisms responsible for NVRs associated with unfavorable IL28B SNPs have not been completely elucidated, ISG expression in patients with unfavorable IL28B genotypes tends to be high at baseline and is insufficiently induced by exogenous IFN administration, resulting in poor treatment outcomes with IFN-based therapy. Even with the introduction of the new class of highly effective DAAAs, IL28B SNPs remain useful predictors of treatment outcomes and can be used to individualize treatment strategies to maximize cost-effectiveness and identify patients at risk of being refractory to treatment due to the emergence of multidrug-resistant HCV.

Conflict of interest

Dr Asahina and Dr Kakinuma belong to a donation-funded department funded by Chugai Pharmaceutical Co., Ltd, Toray Industries, Inc., Bristol-Myers Squibb Company, Dainippon Sumitomo Pharma Co., Ltd., and MSD K.K.

Author contributions

Manuscript writing (YA), critical discussion (MN, SK, MW).

References

[1] Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, et al. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. Hepatology 1990;12:671–675.
fibrosis in patients infected with non-1 HCV genotypes. Hepatology 2012;55:384–394.

[25] Asahina Y, Tsuichiya K, Nishimura T, Muroaoka M, Suzuki Y, Tamaki N, et al. Genetic variation near interferon 28B and the risk of hepatocellular carcinoma in patients with chronic hepatitis C. J Gastroenterol 2013 in press.

[26] Gao DH, Delgiren C, Hammangi OJ, Vends S, Paladrun S, Hartmann R, et al. Interferon-α is functionally an interferon but structurally related to the interferon-10 family. J Biol Chem 2009;284:20869–20875.

[27] Ketenso GV, Gallagger G, Baurin VV, Lewis-Antes A, Shem M, Shah NK, et al. IFN-λ3 mediate antiviral protection through a distinct class II cytokine receptor complex. Nat Immunol 2003;4:69–77.

[28] Shepard F, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Gastroenterol 2003;4:636–638.

[29] Yoshimoto K, Kishida T, Nakano H, Matsui M, Shin-Ya M, Shimada T, et al. Interleukin-28 acts synergistically with cisplatin to suppress the growth of head and neck squamous cell carcinoma. J Immunother 2011;34:139–146.

[30] Morrow MP, Yamanaka K, Pekny P, Sheddok DJ, Lewis MG, Tabott K, et al. IL-28B/IFN-λ3 drives granzyme B loading and significantly increases CTL killing activity in macaques. Mol Ther 2010;18:1714–1723.

[31] Yoshio S, Kanto T, Kuroda S, Motsuba T, Higashitani K, Kikita N, et al. Human BDCA3(-) dendritic cells are a potent producer of IFN-λ in response to hepatitis C virus. Hepatology 2013;57:1705–1715.

[32] Sommeryrens C, Paul S, Staeheli P, Michiels T. IFN-λ3 is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. Plos Pathog 2008;4:e1000017.

[33] Zhang L, Jilg N, Shao RX, Lin W, Fusco DN, Zhao H, et al. IL28 inhibits hepatitis C virus replication through the JAK-STAT pathway. J Hepatol 2011;55:289–298.

[34] Zhou Z, Hammong OJ, Ank N, Paladrun S, Nielsen AL, Hartmann R. Type III interferon (IFN) induces a type I IFN-like response in a restricted subset of cells through signaling pathways involving both the Jak-STAT pathway and the mitogen-activated protein kinases. J Virol 2007;81:7749–7758.

[35] Thomson SJ, Goh FG, Banks H, Krassgruber T, Ketenso SV, Foxwell BM, et al. The role of transposable elements in the regulation of IFN-λ1 gene expression. Proc Nat Acad Sci USA 2009;106:11564–11569.

[36] Marcello T, Grakou A, Barba-Spachet G, Machlin ES, Ketenso SV, MacDonald MR, et al. Interferons alpha and lambda inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. Proc Nat Acad Sci USA 2008;105:11564–11569.

[37] Sugiyama M, Tanaka Y, Wakiha T, Nakanishi M, Miyagishi M, Tanaka T, et al. Interferons alpha and lambda inhibit hepatitis C virus replication. PLoS Pathog 2011;6:e1000863.

[38] Asahina Y, Murakawa M, Sakamoto M, Kakinuma S, Nakagawa M, Azuma S, et al. Impaired IL28B gene induction and poor IL28B promoter activity are associated with the outcome of IFN therapy for chronic hepatitis C. Gastroenterology 2010;139:499–509.

[39] Abe H, Hayes CN, Ochi H, Maekawa T, Tsuge M, Miki D, et al. IL28B inhibition of IL28B gene expression is a stronger predictor of treatment response than IL28B genotype in patients with hepatitis C. Gastroenterology 2011;140:1021–1031.

[40] Asahina Y, Tsuichiya K, Muroaoka M, Tanaka K, Suzuki Y, Tamaki N, et al. Assocation of gene expression involving innate immunity and genetic variation in interleukin 28B with antiviral response. Hepatology 2012;55:20–29.

[41] Honda M, Sakai A, Yamashita T, Nakamoto Y, Mizukoshi E, Sakai Y, et al. Impaired ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. Gastroenterology 2010;139:499–509.

[42] Abe H, Hayes CN, Ochi H, Maekawa T, Tsuge M, Miki D, et al. IL28B inhibition of IL28B gene expression is a stronger predictor of treatment response than IL28B genotype in patients with hepatitis C. Gastroenterology 2011;140:1021–1031.

[43] Asahina Y, Tsuichiya K, Muroaoka M, Tanaka K, Suzuki Y, Tamaki N, et al. Association of gene expression involving innate immunity and genetic variation in interleukin 28B with antiviral response. Hepatology 2012;55:20–29.

[44] Honda M, Sakai A, Yamashita T, Nakamoto Y, Mizukoshi E, Sakai Y, et al. Impaired ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. Gastroenterology 2010;139:499–509.

[45] Gane EJ, Stedman CA, Hyland RH, Ding X, Pang PS, Symonds WT, et al. All-oral sofosbuvir-based 12-week regimen for the treatment of chronic HCV GT1 infection: results from the AVIATOR study. J Hepatol 2013;58:5570–5579.

[46] Gane EJ, Stedman CA, Hyland RH, Ding X, Pang PS, Symonds WT, et al. All-oral sofosbuvir-based 12-week regimen for the treatment of chronic HCV GT1 infection: results from the AVIATOR study. J Hepatol 2013;58:5570–5579.