MINI REVIEW

IL28B polymorphisms and chronic hepatitis C

Polymorphisme de l’IL28B et hepatite chronique C

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Summary  Human genetic factors that influence HCV treatment responses have been identified by a recent landmark discovery. A SNP has been identified (rs12979860) located in chromosome 19, 3 kb upstream of the IL28B gene that encodes IFN-\(\lambda\)3, which was strongly associated with the sustained virological response (SVR) to pegIFN and ribavirin in more than 1000 patients with genotype 1 chronic hepatitis C. In patients of European ancestry, as well as in African-American and Hispanic patients, the CC genotype was associated with a two-fold greater SVR rate than the TT genotype, CT being closer to TT than to CC. More information is now needed to understand the mechanisms that underlie this association.

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Résumé  Récemment, un facteur génétique associé à la réponse virologique a été mis en évidence chez les malades ayant une hépatite chronique C de génotype 1. Un polymorphisme (rs12979860) situé sur le chromosome 19, en amont du gène IL28B qui code pour l’IFN-\(\lambda\)3, a été identifié comme fortement lié à la réponse virologique soutenue (RVS) chez plus de 1000 malades traités par pegIFN et ribavirine. Chez les malades caucasiens, comme pour les afro-américains et hispaniques, le génotype CC était associé à une probabilité de RVS deux fois plus importante que pour les génotypes TT ou CT. D’autres études doivent être menées pour comprendre le mécanisme impliqué dans cette observation.

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Worldwide, 130 to 170 million people are chronically infected with hepatitis C virus (HCV), and up to 20% of them will develop liver complications, including cirrhosis, end-stage-liver-disease and hepatocellular carcinoma. Chronic hepatitis C is curable by antiviral therapy. The current standard of care for patients with chronic hepatitis C is the combination of pegylated interferon (pegIFN) alpha-2a or -2b and ribavirin. Approximately 40–50% of patients are infected with HCV genotype 1 and 80% of those infected with genotypes 2 and 3 clear infection with this therapy. Interferon is thought to work mainly by stimulating host’s natural defenses against the viral infection, including antiviral effectors within infected cells and the adaptive immune response; the mechanisms of action of ribavirin are not completely understood. Several factors have been identified to play a role in the outcome of therapy, including the treatment schedule, disease characteristics, viral factors, and host factors. However, these factors only partly explain the ability of IFN and ribavirin therapy to cure HCV infection.

Human genetic factors that influence HCV treatment responses have been identified by a recent landmark discovery. A new methodology in genetics, genome-wide association study (GWAS), has been used to identify single nucleotide polymorphisms (SNPs) associated with a cure of HCV infection on IFN-ribavirin therapy. The principle of GWAS is to test the association of a characteristic of interest, usually a disease, typically with hundreds of thousands of SNPs. The power of GWAS to detect associations results of the large number of variants screened and depends on the number of patients included in the study. Ge and colleagues identified a SNP (rs12979860) located in chromosome 19, 3 kb upstream of the \textit{IL28B} gene that encodes IFN-\gamma, which was strongly associated with the sustained virological response (SVR) to pegIFN and ribavirin in more than 1000 patients with chronic genotype 1 infection from the IDEAL trial [1]. In patients of European ancestry, as well as in African-American and Hispanic patients, the CC genotype was associated with a two-fold greater SVR rate than the TT genotype (Fig. 1), CT being closer to TT than to CC. The relationship between this polymorphism and the SVR explained much of the difference in the response between European-American and African-American patients, as the T allele is significantly more frequent in the latter than in the former [2]. Two other GWAS-based studies have independently confirmed these results in patients infected with genotype 1 and genotypes 2 and 3 [3—6]. In addition, an overlapping group of SNPs located in the same region of chromosome 19 has been identified to be associated with the response in different populations of European and Japanese origin. Although all of the identified variants lie in or near the \textit{IL28B} gene, an effect on the function of this gene has not been demonstrated and the molecular mechanisms that underlie the relationship remain unknown. A higher expression of \textit{IL28A} and \textit{IL28B} in whole blood has been observed in patients with a responder haplotype than those with a non-responder one (SNP rs8099917, TT or GT versus GG, \textit{P} < 0.05), but the meaning of this finding remains obscure [3]. \textit{IL28B} polymorphisms have been shown to influence on-treatment viral kinetics, as they appear to be associated only with the first phase of viral decline during pegIFN—ribavirin therapy [7]. This indicates that they are linked to a genetic predisposition to respond to IFN administration by mounting an efficient antiviral response. An intriguing finding was the significantly different distribution of SNP, rs12979860 \textit{IL28B} alleles CC in Caucasian patients infected with different genotypes (55% in genotype 3, 46% in genotype 2 and 33.5% in genotype 1, \textit{P} < 0.001) [5].

A large number of studies have been presented at the last EASL annual meeting in Vienna on \textit{IL28B} polymorphisms and their predictive role on the SVR to current therapies.
standard treatment. They are all largely confirmatory of the initial reports. Among them, a retrospective analysis of patients infected with HCV genotypes 2 or 3 treated with variable durations of standard treatment showed that SNP rs12979860 genotype was the strongest predictor of SVR only in patients with a rapid virological response [8]. In addition, a retrospective analysis of two multinational phase II trials in treatment-naïve patients and previous non-responders infected with HCV genotypes 1 or 4 has shown that two nucleotide polymorphisms (SNPs rs12979860 and rs809917) were independently associated with the SVR [9].

More information is now needed to understand the mechanisms that underlie the association. One product of the IL28B gene, IFN-λ3, triggers an antiviral cascade via the Jak-Stat signaling pathway that is similar to, and probably synergistic with that of type I interferons, although it uses a distinct receptor [10]. Like type I interferons, lambda interferons have antiviral activity against HCV both in vitro and in vivo. Exogenous administration of lambda interferon is associated with a slower but more sustained induction of interferon-stimulated genes (ISGs) than alpha interferon [11]. However, the SNP rs12979860 and rs8099917 alleles associated with a lower chance of an SVR were also significantly associated with an increased expression of ISGs and an unexpected decreased expression of IL28B. This finding suggests no direct link between altered IFN-λ3 expression and preactivation of the endogenous IFN system in the liver, while hepatic ISG expression appeared to be the best predictor of treatment responses [12].

In summary, genetic variations upstream of the IL28B gene have been shown to be associated with the response to standard-of-care therapy in HCV monoinfected patients, but the underlying mechanisms remain unknown. Their identification can be used as a predictive marker of the response, but the individual predictive value of each SNP is not very high, thus its use in clinical practice should be cautious. The impact of host genetic polymorphisms on hepatitis C treatment outcomes in special populations, such as HIV/HCV-coinfected patients, and on the combination of pegIFN, ribavirin and direct acting antivirals has to be determined. Future studies will be needed to understand the underlying mechanisms and derive treatment strategies that use pretreatment characterization of host genetics.

Conflict of interest statement

No conflict of interest with the manuscript.

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References