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Host Factors to Predict Treatment Response in HCV Patients: Implications for Individualized Therapy and Translational Medicine for HCV Management

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Hepatitis C virus (HCV) infection is a major health problem, affecting more than 170 million peolpe worldwide, representing 3% of the world's population [1,2]. It is the most common newly diagnosed cause of liver disease and the most common indication for a liver transplant in North American and in Europe [3]. Treatment of chronic hepatitis C virus (CHC) infection is difficult: current standard of care is pegylated-interferon α (PegIFN) combined with ribavirin [4]. However, the overall response rate is only 50% and it is always associated with high costs and serious side effects [1,5-7].

In most cases (60-85%), HCV infection progresses to chronic liver disease, which can lead to liver cirrhosis and hepatocellular carcinoma (HCC) [8]. Although new treatment options with drugs which inhibit viral enzymes (e.g. protease and polymerase inhibitors) are under development and some are already in clinical use, preliminary data indicate that, if these Direct-acting Antivirals (DAAs) are used alone, HCV mutates rapidly to develop resistance. Therefore, even in the presence of DAA, interferon (IFN) will still remain as a backbone for the combination therapy in the foreseeable future [9].

Due to the fact that almost half of the patients fail to respond to IFN-based therapy, patients would benefit from a prognostic tool to predict the likelihood of a treatment response prior to the initiation of therapy, or at least soon after starting therapy. A number of host and viral factors may help predict who is more or less likely to achieve a sustained virological response (SVR, defined as undetectable of serum HCV RNA 6 months after termination of therapy), but new strategies are being developed that may significantly enhance our ability to predict treatment response [5,10].

One example of these new techniques is high throughput gene expression profiling, which looked at the effects of HCV infection in the host liver at the whole genomic level. For example, Chen et al. [10] used a 19,000 cDNA microarray to study pretreatment liver biopsy specimens taken from patients with chronic HCV who were subsequently treated with combination therapy with PegIFN/RBV. Gene expression levels of 19,000 host genes were compared among 15 non-responder, 16 responder and 20 normal liver biopsy specimens. They identified 18 genes whose expression levels differed consistently between responders and non-responders, and demonstrated that the 18 gene signature has a positive prediction value (PPV) of at least 95% for predicting those patients who are likely to achieve SVR [10,11].

Genome-wide association studies (GWAS) allow an unbiased sampling of variations in genes across the entire genome without a hypothesis. Using GWAS, four groups reported that a single-nucleotide polymorphism (SNP) at roughly 3kb upstream of the promoter region of IL28B gene (which encodes a type III IFNλ3) is associated with both treatment-induced and spontaneous HCV clearance [12,13]. Ge et al. [12] studied more than 500,000 SNPs and found that SNP rs12979860 was strongly associated with treatment induced SVR. This SNP was also found to be associated with virus spontaneous clearance [13].

Previous studies have clearly shown that both host and viral factors were associated with response to the current standard therapy with pegylated IFN and Ribavirin in patients with CHC. The demographics of patients such as age, gender, body mass index (BMI), fibrosis stage and insulin resistance have been reported to be predictive of response [14-17]. Viral factors negatively influence likelihood of achieving SVR include HCV genotype 1, high pretreatment viral load, viral kinetics (slow decline) during treatment [18-21], as well as certain amino acid mutations in viral proteins, such as NS5A [22]. Moreover, the high rate of PegIFN/RBV therapy failure and ethnic contribution to treatment response indicate that host genetic factors, in addition to patient demorgraphics and viral factors, also play an important role in determining the antiviral outcomes.

Pretreatment Hepatic ISG Expression and Treatment Response

Several studies identified that the increased expression of a group of hepatic genes, most of which are IFN stimulated (sensitive) genes (ISGs) was associated with treatment failure [11,23-26]. For instance, Chen et al. [10,11] identified an 18-gene signature that differentiated treatment responders from non-responders with a positive predicting value of 96%. Using real-time PCR analysis, Asselah et al. [26] also found 3 ISGs (IFI-6-16, IFI27 and ISG15) whose increased expression at baseline was correlated with poor response in two independent cohorts. Significant positive association between the pretreatment"high ISG" phenotype and unfavorable treatment outcome was confirmed by many other studies [23-25]. Although ISGs expressed strongly in NRs before treatment, similar levels of ISGs expressions were observed in both Rs and NRs/ ETRs on treatment, suggesting that maybe not ISGs expression itself, but changes before and after treatment influenced the response outcomes [23-25]. Importantly, given the fact that patients infected with HCV genotype 2 or 3 have a higher SVR rate, the finding that baseline hepatic ISG expression was significantly lower in subjects infected with HCV gennotype 2 and 3 than with genotype 1 and 4 indicated that pretreatment activation of IFN-α system

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may be correlated with HCV genotypes [24]. Whatever the reason, endogenous activated ISGs in chronic HCV may be a biomarker of immune dysfunction rather than antiviral effect of IFN-α. It has now been generally agreed that preactivation of IFN-αsignaling in the pretreatment HCV-infecetd liver tissues leading to the increased expression of a subset of ISGs is associated with treatment non-response (failure), although the mechanisms remain to be determined. A few recent studies provided some clues to understanding and elucidating possible mechanisms [11,27]. Most recently, it has been shown that blocking type I IFN signaling by IFNAR antibody cures persistent LCMV infection, indicating that too much activation of the IFN signaling may contribute to chronic persistent viral infections [28,29].

Host IL28B SNP and Treatment Response

Other studies directed at exploring the association between single nucleotide polymorphisms (SNPs), which is one of the most common forms of host gene variation, and treatment outcomes with pegylated IFN and Ribavirin. These studies make it possible to develop genomics-based approaches for predicting treatment responses.

Recent independent genome-wide association studies (GWAS) revealed that some SNPs around *IL28B* on chromosome 19 which codes for interleukin 28B (IFN- λ3) is associated with both treatment-induced and spontneous HCV clerance [12,13].

The first HCV GWAS study involving 871 European, 191 African and 75 Hispanics infected with genotype 1 HCV showed that rs12979860 (located ~3 kb upstream of IL28B promoter region) was associated with a twofold increase in SVR rate [12]. Interestingly, this variant was found to be in linkage disequilibrium with rs8099917 (located ~8kb upstream of IL28B and ~16 kb upstream from IL28A) in European more than in African population in this compliant cohort. A further 67 individuals from another clinical trial were enrolled to compared the effectiveness of PEG-RBV between African-Americans and European-Americans, substantiating the discovery in a population with extremely well-characterized phenotypes. Tanaka et al. [30] investigated genetic predictors through a two-stage design, the first stage of GWAS in 154 Japanese with HCV genotype 1 , and the second replication stage in a independent population of 172 patients. Strongest association was observed with SVR for rs8099917 and rs12980275 in both stages. In addition, 6 other SNPs also achieved the suggestive genome-wide threshold in both the GWAS cohort and replication cohort. Suppiah et al. [31] also used a two-stage approach consisting of an initial GWAS stage in 293 Australian and a followed replication (confirmation) stage in Western European. They identified rs8099917 as the variant most strongly associated with SVR. The fourth GWAS was conducted in genotype 1 or 4 HCV-infected subjects of Europe origin [32]. Moreover, this study was extended to both HCV mono- and HCV/HIV co-infected populations. In their study, the minor allele of rs8099917 was identified in 58% of patients who failed to respond, and defined as a risk factor associated with progression to chronic HCV infection, regardless of co-infected with HIV or not. Ochi et al. [33] confirmed IL28B polymorphism association with SVR in Asian population infected with HCV genotype 1b or 2a. Two SNPs (rs8099917 and rs12979860) in IL28B have been confirmed to be associated with the outcome of PEG-RBV combination and IFN monotherapy. Furthermore, they found that combination of 4 novel SNPs showed more power in predicting treatment outcomes than any single variant.

Taken together, all the above mentioned studies confirmed that genetic variation close to the IL28B region was associated with both treatment-induced and spontaneous HCV clearance.

Based on the data acquired from GWAS, targeted studies were performed using a candidate gene approach, in which particular polymorphisms of IL28B are chosen to be tested for association with treatment efficacy. It was reported by Mangia et al. [34] that IL28B genotype (rs12979860) CC is associated with more successful treatment outcomes in the whole studied population. Some other studies found similar results [18,20]. Interestingly, both Mangia et al. [34] and Thompson et al. [19] observed that the rs12979860 was a better predictor for SVR especially among patients without rapid virologic response (RVR, defined as undetectable HCV RNA at week 4 after beginning of therapy). In addition, a study of Caucasians and African American indicated that predicting power of rs12979860 may be race-dependent [35].

Therefore, these studies confirmed a significant association between IL28B genetic variation and treatment outcomes.

Correlation between Hepatic ISG Expression and IL28B SNPs

At present, two best host factors to be able to predict treatment outcomes in HCV infected patients are baseline (pretreatment) hepatic ISG expression and IL28B SNPs. This attracts a lot of interest to determine whether they are independent predictors or linked together. The possible association between the hepatic ISG expression and SNPs of IL28B stemmed not only from their common predictive effects on treatment outcomes in patients infected with HCV, but more possibly from the fact that the downstream signaling pathway of IL28B(IFNλ3) receptor contains the same kinases (JAK1 and Tyk2) and transcription factors IFN-stimulated gene factor 3 (ISGF3) as that of IFN-α receptor, and results in up-regulated expression of type I IFN-like gene transcription profile [36]. Some observations provide convincing evidence for this possible association. For instance, Honda et al. [37] reported that hepatic ISG expressions were up-regulated in Japanese chronic hepatitis C patients with the unfavorable rs8099917 genotype (TG or GG). In an American population, Urban et al. [38] also validated the correlation between high pretreatment ISGs and minor (unfavourable) rs12979860 genotype.

Because both rs8099917 and rs12979860 lie in the upstream region of IL28B gene, it is likely that they may influence IL28B transcription and synthesis. Studies from Tanaka et al. [30] and Suppiah et al. [31] support this hypothesis. Results from 20 HCV paitents and 49 healthy volunteers indicated that lower IL28B mRNA level in individuals with miner G allele of rs8099917.

However, another intersting study indicated that IL28B genotype and ISGs level are independent predictors of SVR [39]. In this study, the authors measured variation of IL28B SNP (rs8099917 and rs12979860) and quantified the ISGs expression in liver biopsies from 109 Caucasian patients with chronic hepatitis C, and concluded that the variations of IL28B gene could not determine the hepatic ISGs expression and alluded that IL28B genotype and pre-treatment hepatic ISGs level are independent predictors of SVR.

Future Directions

With the newly developed DAAs in clinical use, current standard therapy for CHC is triple therapy with pegylated IFN, ribavirin and one of the HCV protease or polymerase inhiitors. This triple therapy increased SVR up to 75%. Although interferon-free regimen is being

developed and in clinical trial, it is most likely that intereron will remain as backbone and essential component for triple therapy due to the rapid emergence of viral resistant mutants if DAA is used alone. Prediction of treatment outcomes will tailor the treatment to invidual patient and faciliatate the adoption of personalinzed medicine in the treatment of chronic HCV infection.

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