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In the Literature

Genetic Determinants of Outcomes in Chronic Hepatitis C Virus (HCV) Infection

Ge D, Fellay J,Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399–401.

Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009;41: 1100–1104.

Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105–1109.

Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009; 461:798–801.

The variability among patients in their response to therapy of chronic HCV infection has remained largely unexplained. The IDEAL study randomized 3070 treatment-naive patients with chronic infection due to HCV genotype 1 to receive either interferon-alfa-2a or interferon-alfa-2b at 1 of 2 doses, with all subjects also receiving ribavirin [1]. There was no significant difference between the treatment groups in the incidence of sustained virological response, which ranged from 38.0% to 40.9%. Consistent with previous findings, however, the odds ratio for sustained virological response in white persons versus African American persons was 3.039 ($P < .001$). The reason for the significantly impaired therapeutic response of individuals of African ancestry relative to those of European ancestry has been unknown, but the IDEAL study provided an opportunity for Ge and colleagues to perform a genome-wide association study on >1000 subjects from that study, as well as an additional 67 subjects from another prospective treatment trial. They detected a polymorphism on chromosome 19q13 that is 3 kb upstream of the *IL28B* gene that was associated with a 2-fold difference in treatment response in both those of European ancestry and those of African-American ancestry. The favorable polymorphism (C/C) is more prevalent among those of European ancestry than among African Americans, and it was estimated that this polymorphism accounts for approximately one-half of the difference in response rates between the 2 populations.

Two other groups of investigators also applied genome-wide association in examining this issue in different patient cohorts—patients of European origin in the study by Suppiah and colleagues and Japanese patients in the study by Tanaka and colleagues. Both groups also identified polymorphisms in proximity to the *IL28B* gene as predictors of response to treatment of chronic HCV infection. Although the polmorphisms identified by both the study by Tanaka and colleagues and the study by Suppiah and colleagues differed from those found by Ge and colleagues, both were in physical proximity upstream of the *IL28B* gene, and the 2 distinct polymorphisms are in linkage disequilibrium, especially in European populations.

In addition to differences in treatment response, there are also significant differences in spontaneous clearance of HCV infection among different population groups. It turns out that polymorphisms adjacent to the *IL28B* gene not only play a role in determining the response to therapy of chronic HCV infection, they also play a role in immune clearance of the infection. Overall, ~30% of individuals spontaneously clear HCV infection, but there is significant variability depending on ethnic background, with such clearance occurring in ~36% of individuals of non-African ancestry but in only 9% of those with an African genetic background. The C/C genotype is present in 30%–50% of sub-Saharan Africans and in ~90% of Chinese and Japanese persons, with an intermediate figure for Americans of European ancestry. Thomas and colleagues have now demonstrated that genetic variation in the *IL28N* gene is an important factor in predicting clearance of HCV and accounts for a significant portion of the variability in clearance among groups.

Interferon-λ-3 (L28B) is a type III interferon. The type III interferons (interferon λ-1, interferon λ-2, and interferon λ-3) are encoded by *IL29, IL28A,* and *IL28B,* respectively. Although interferon-λ binds to a receptor distinct from that of interferon-α, a type I interferon, their effects each flow through the same JAK-STAT activation pathway. Interferon-λ has activity against HCV (and human immunodeficiency virus) in vitro.

Thus, there is clear evidence indicating that genetic variation in the gene encoding interferon-λ-3 is highly predictive of both spontaneous and therapy-induced clearance of HCV infection. This may prove of great value in making decisions regarding the institution and continuation of existing therapies and may also provide a new therapeutic agent. One potential benefit of therapy with interferon-λ may be reduced toxicity, because in contrast to interferon-α, hematopoietic cells lack receptors for interferon-λ, suggesting that therapeutic administration of the latter may be associated with less related toxicity. In a Phase 1b study of patients with relapsed chronic HCV genotype 1 infection, in a small number of patients, pegylated interferon-λ-1A (PEG-IFN-λ and PEG-rIL-29) demonstrated potent antiviral effect, with undetectable plasma HCV RNA achieved by 3 of 6 patients in one dosing group [2].

References

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