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The role of genetics in hepatic fibrosis amongst HCV patients

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Progression to liver fibrosis and cirrhosis is a common pathway into which inflammatory liver diseases of many etiologies converge. Chronic hepatitis C virus (HCV) infection alone places more than 170 million people worldwide at risk of developing fibrosis and cirrhosis. While the progression of liver disease is a multifactorial process, polymorphisms in the type III IFN locus on chromosome 19 are associated with disease progression. A study by Eslam et al. identifies the rs12979860 [CC] genotype as a strong predictor of tissue inflammation and fibrosis in HCV-infected patients (1). Paradoxically, this genotype is also a favorable predictor of spontaneous HCV clearance and response to treatment [reviewed in (2)]. This suggests that mechanisms that are beneficial to the host in resolving HCV infection, become detrimental if the virus cannot be cleared and establishes chronic infection.

Because of its proximity to the *IFNL3* (IL28B) gene, the non-functional rs12979860 genetic marker was considered an IL28B variant until Prokunina-Olssen et al. established in 2013 that rs12979860 is actually located in the first intron of the newly identified *IFNL4* gene (3). IFN λ 4 protein expression is regulated by another polymorphism (rs368234815), located 367 base pairs upstream of rs12979860. The rs368234815 [G] allele creates an open reading frame for the IFN λ 4 protein whereas the rs368234815 [TT] allele results in a frameshift and does not produce IFN λ 4 protein (3). rs12979860 and rs368234815 are in strong linkage disequilibrium and predict HCV clearance almost equally well in Europeans, but are in weaker disequilibrium with a higher predictive value of rs368234815 for HCV clearance in African Americans (3).

In their recent study, Eslam et al. evaluate the relative roles of rs12979860 and rs368234815 in liver inflammation and fibrosis (4). They also evaluate two additional polymorphisms, rs4803217 and rs117648444, that affect *IFNL3* and *IFNL4* activity, respectively. rs4803217 is located in the 3' untranslated region of *IFNL3* and regulates *IFNL3* mRNA stability by altering the binding of miRNAs (5). rs117648444 [C → T] causes a proline to serine substitution at amino acid position 70 of the IFN λ 4 protein and thereby alters the antiviral function of the expressed IFN λ 4 protein (6). This is consistent with the results of clinical studies: patients with the IFN λ 4-S70 variant have lower intrahepatic expression of interferon stimulated genes (ISGs), and higher rates of spontaneous HCV clearance and response to interferon-based treatment than patients with the active IFN λ 4-P70 variant.

However, their HCV clearance rate is still lower than that of patients who do not carry the rs368234815 [G] allele and therefore produce neither IFN λ 4-P70 nor IFN λ 4-S70 (6). These findings suggest that the rs117648444 [C $\rightarrow$ T] genotype partially counteracts the negative effect of the rs368234815 [G] genotype.

Evaluating liver biopsies of 1923 Caucasians with chronic HCV infection with the Metavir scoring system, Eslam et al. classify a Metavir inflammatory score of equal or greater than A2 (moderate histologic activity) as severe inflammation and a Metavir fibrosis score of equal or greater than F2 (enlargement of portal tract with rare septa formation) as severe fibrosis (4). For a subgroup of 1003 patients for which an approximate HCV infection date is known, the authors calculate the liver fibrosis progression rate as the ratio between fibrosis stage and estimated years of infection. They find that rs12979860 [CC], rs36823481[TT] and rs4803217[GG] are strongly associated with significant inflammation and fibrosis and fast fibrosis progression rate. The associations remain significant after adjusting for factors, such as sex, age, body mass index, recruitment center, liver enzymes, diabetes mellitus, HCV genotype and alcohol intake, that also contribute to disease progression. The authors state that the rs117648444 genotype, which encodes IFN λ 4-S70, does not affect these features.

To explore the mechanisms of disease progression, Eslam et al. then assess the frequency of intrahepatic immune cells in the context of the rs12979860 and rs117648444 genotypes. Intrahepatic T cells (CD3+ and CD8+ cells) and macrophages (CD163+ cells) are more abundant in livers of patients with the rs12979860 [CC] genotype compared to those with the rs12979860 [CT] or [TT] genotypes but are not affected by the rs117648444 [C/T] genotype. The same observation is made for the serum level of sCD163, a marker for macrophage activation. Hepatic inflammation and fibrosis correlate with *IFNL3* mRNA levels in the liver biopsies. The authors conclude that IFN λ 3 rather than IFN λ 4, likely mediates *IFNL3-IFNL4* haplotype-associated hepatic inflammation and fibrosis in patients with chronic HCV infection.

While Eslam et al. confirm their exciting earlier study linking IFN- λ genotype to fibrosis risk (1), it remains difficult to assign differential risks to individual genetic variants in the IFN- λ region because of the strong linkage disequilibrium between these polymorphisms among Caucasians. Rs12979860 is a non-functional genetic marker in close physical proximity to the *IFNL3* gene and in strong linkage disequilibrium with the functional rs368234815 that controls IFN- λ 4 protein expression. If IFN- λ 3 was key to fibrosis risk, the functional *IFNL3* variant (rs4803217) might be more strongly associated with fibrosis than rs368234815, but linkage disequilibrium between these variants limits that comparison in this exclusively Caucasian population (1). It would, therefore, be important to extend the study to an African American population where linkage disequilibrium between these polymorphisms is lower and significant differences between rs12979860 and rs368234815 genotypes as predictors of HCV clearance are known (3). This is consistent with a study by Aiken et al. who reports that the rs368234815 genotype is more strongly associated with the development of early post-transplant fibrosis than the rs12979860 genotype in a cohort of HCV-infected organ recipients that includes 19% African Americans (7). However, given that African Americans with chronic HCV infection have a slow disease progression rate,

that fibrosis progression is not linear over time and that the effect of the rs12979860 [CC] genotype on liver fibrosis progression is stronger at early fibrosis transitions (F0 to F1 and F1 to F2) (1) it is important to define as closely as possible the time point at which early fibrosis stages are reached. Ideally, this is based on histological results from two biopsies.

While quantitation of *IFNL4* mRNA is difficult due to its low abundance and the presence of splice variants, it would be important to include *IFNL4* mRNA quantitation to provide information of the functional interplay of *IFNL3* and *IFNL4* in liver fibrosis. Further, quantitation of *IFNL1* mRNA would help determine whether the correlation with fibrosis is specific to *IFNL3*. Because both IFN- λ polymorphisms and ISG expression are associated with a beneficial response to interferon-based therapies in chronic HCV infection (2), it would also be helpful to quantitate ISG and IFN λ receptor expression. In this context, Petta et al. demonstrate an association of the rs12979860 [CC] and rs36823481 [TT] genotypes with reduced intrahepatic ISG expression, severe lobular necroinflammation and F3-F4 fibrosis (8). Combined with the results by Eslam et al (1, 4), the data point to a role of reduced intrahepatic ISG expression in liver disease progression. An analysis of cytokines related to inflammation and fibrosis (e.g. PDGF, CTGFL-6, TNF- α , IFN- γ , TFG- β 1 and PDGF) may help elucidate the role of IFN λ s in this process and identify targets for therapeutic intervention to decrease the rate of fibrosis progression and the risk of developing end-stage liver disease.

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