In HIV/HCV Coinfected Patients Dendritic Cell Activation State Is Not Associated With IL28B Genotype

Anti-hepatitis C virus (HCV) treatment in patients infected with human immunodeficiency virus (HIV) has become a focus of recent clinical investigations. HCV treatment efficacy appears to be dependent on the patient’s immunological status at the baseline, with the response rate being directly proportional to the pretreatment CD4 cell count [1, 2]. In HCV monoinfected individuals, a strong association between allelic variants of IL28B gene encoding interferon λ3 (IFNλ3) and response to pegylated interferon alfa (peg-IFN-α) and ribavirin (RBV) treatment was reported. Failure to respond to treatment was associated with minor allele rs2979860 (T) [3]. This association has been replicated in the setting of HIV/HCV co-infection [4], where the good response IL28B genotype was associated with higher rates of sustained virological response (SVR), compared with poor-response variants. However, the functional role of IL28B in HCV pathogenesis and therapy outcome remains unknown.

Anthony and colleagues recently reported interesting data regarding the association between soluble CD14 (sCD14) and CD16+CD56− natural killer (NK) cells with response to IFN/RBV therapy in HIV/HCV genotype 1 coinfected patients [5]. They found that baseline plasma sCD14 and CD16+CD56− NK cell frequencies were negatively associated with the magnitude of HCV load decline at weeks 4 and 24 and with SVR, suggesting that this marker of immune activation is a negative predictor of successful therapy. However, no correlation was observed between sCD14 or CD16+CD56− NK cells and IL28B genotype. Recently, we found that the baseline activation state of circulating plasmacytoid dendritic cell (pDC), from HIV/HCV coinfected patients (including genotypes 1, 2, 3, 4), correlates with therapy efficacy, including early virological response (EVR) and SVR. Moreover, IFN-α treatment induced the up-regulation of the activation state of pDC and myeloid DC (mDC) in both EVR and SVR, but not in non-EVR and non-SVR [6]. These data suggest that in HIV/HCV coinfected individuals, a high baseline maturation level of pDC may indicate their exhaustion and subsequent inability to respond to further IFN-α stimulation, confirming in these cells the impairment of IFN-α system. In the same patients we evaluated the IL28B favorable genotype (rs12979860) and observed that the favorable IL28B genotype was not correlated with HCV decline after 4 week of treatment (1.15 ± 0.3 in C/C, 1.25 ± 0.3 in C/T).

Figure 1. CD80 and CD86 expression on pDC from HCV/HIV coinfected patients analyzed by flow cytometry. Here pDC were defined as Lin1−/HLA−DR+/CD11c−. In this gate, the expression of CD80 (A) and CD86 (B) was analyzed. Patients (19) are grouped as IL28B rs12979860 major allele (CC) and IL28B rs12979860 minor alleles (CT/TT). CD80 and CD86 expression on pDC from HCV/HIV coinfected patients analyzed by flow cytometry. Genotyping of the SNP rs12979860 was performed using a TaqMan 5′ allelic discrimination assay (Applied Biosystems, Forster City, CA). The primers sequences were 5′ GCC TGT CGT GTA CTG AAC CA 3′ and 5′ GCC CGG AGT GCA ATT CAA C 3′. The TaqMan probes were VIC- TGG TTC GCG CCT TC-MGB and FAM-CTG GTT CAC GCC TTC-MGB. CD80 (C) and CD86 (D) expression on pDC was evaluated after exclusion of HCV genotypes 2 and 3 infected subjects. Data are represented as percentage of %pDC CD80+ or CD86+ ±SE. Statistical evaluation of the differences between groups was based on nonparametric test (Mann–Whitney). No statistically significant differences were observed. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; pDC, plasmacytoid dendritic cell; SNP, single-nucleotide polymorphism.
and T/T groups). Moreover, as described by Anthony et al [5] for sCD14, the baseline activation state of pDC subset (evaluated as CD80 and CD86 expression) did not associate with IL28B genotype (Figure 1A and 1B). Similar results were obtained for mDC (data not shown). Because it was suggested that in patients infected with HCV genotypes 2 and 3, the absolute effect of IL28B genotype on SVR is weaker than genotypes 1 and 4 HCV [7], to exclude a potential confounding factor, we also analyzed our data after exclusion of HCV genotypes 2 and 3. In HIV/HCV genotype 1 and 4 infected patients, HCV decline after 4 weeks of treatment was higher in the IL28B favorable group compared to the unfavorable group (0.98 ± 0.12 vs 0.37 ± 0.08, P = .01). However, again no association was observed between IL28B polymorphism and pDC activation (Figure1C and 1D) or mDC activation (data not shown). Overall, these data confirm that the immune activation observed in patients who do not achieve EVR or SVR is independent from IL28B polymorphism. IFNs inhibit HCV replication in vivo and in vitro by inducing IFN stimulated genes (ISG) [8]. Patterns of intrahepatic ISG expression differ by IL28B genotype, where the good response IL28B genotype is associated with low-level ISG expression, consistent with the observation that low levels of liver ISG predicts rapid IFN treatment response [9]. However, more recently, Dill and colleagues [10], by stratifying patients according to treatment response, have shown that IL28B genotype and hepatic ISG expression are not directly related but rather are independent predictors of SVR. Altogether, these data indicate that the activation of the innate immune system observed in nonresponders is not linked to IL28B, thus making necessary more detailed studies to clarify the complex interactions between peg-IFN/RBV treatment and the components of the immune system during HCV mono-infection and HIV/HCV infections.

Notes

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