CONTROL ID: 1741437

TITLE: IL28B genotype defines differential immune costimulatory receptor expression in acute hepatitis C

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ABSTRACT BODY: Background: Single-nucleotide polymorphism (SNPs) near IL28B gene is strongly associated to hepatitis C virus (HCV) clearance, both in acute infection and with IFN-based therapy. T cells also play a key role in natural HCV clearance. In this study, we hypothesized that IL28B genotype defines the level at which T cell costimulatory pathways are induced during acute hepatitis C (aHCV), thereby contributing to virological outcomes. To test this hypothesis, we examined the phenotype of circulating T cells in aHCV patients relative to IL28B genotypes.
Method: Twenty one patients with aHCV were enrolled with IRB-approved informed consent between 2000-2012, and included based on available cryopreserved peripheral blood lymphocytes (PBL) collected within 24 weeks from clinical aHCV onset. aHCV was diagnosed by HCV viremia and acute ALT elevation with documented HCV seroconversion and/or 10-fold HCV-RNA fluctuation, excluding HIV-infected persons. IL28B genotype was deteremined by TaqMan real-time PCR. PBMCs were examined for immune markers including FoxP3, PD-1, CTLA-4, CD28 and CD127 in multi-parameter flow cytometry. Demographic, clinical and immune parameters in patients with IL28B CC and non-CC genotype were compared, using non-parametric statistics.
Result: Our aHCV cohort (12 CC, 9 non-CC) were mostly males in their 30-40's, predominantly white (76%) with HCV genotype 1 infection (86%) with similar peak ALT activity (1010 CC vs 978 Non-CC U/L) and HCV RNA titers (log 6.9 CC vs 5.8 Non-CC). CC patients displayed greater viral clearance (+/- therapy) than non-CC patients (75% vs 22%, p=0.03). As for immune parameters, CC and Non-CC patients were similar in %CD3, %CD4, %CD8 or %FoxP3+ Tregs. However, CD8 (but not CD4) T cells from non-CC patients displayed greater expression of positive costimulatory receptors CD28 (54% CC vs 72% non-CC, p=0.047) and CD127 (43% CC vs 74% non-CC, p=0.002) without significant differences in PD-1 or CTLA-4 expression. Of interest, ALT activity correlated positively with CD28 (R=0.67, p=0.049) and CD127 (R=0.70, p=0.04) in CD8 T cells, but only in Non-CC patients. Similarly, HCV RNA titers correlated positively with CD28 (R=0.74, p=0.04) and CD127 (R=0.71, p=0.046) only in Non-CC patients. Significant positive associations were also observed for CD28 and CD127 in CD4 T cells and ALT (CD28: R=0.84, p=0.005; CD127: R=0.88, p=0.002) or HCV RNA (CD28: R=0.91; p=0.002, CD127: R=0.76, p=0.03), but only in Non-CC patients.
Conclusion: We conclude that IL28B genotype contributes to differential regulation of immune costimulation during acute hepatitis C. Functional relevance of these findings is currently under investigation.