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Abstracts, 4th DICID

Free Paper Presentation 1: HCV & HIV

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PL-001 USP18 stimulates HCV production and blunts the antiviral effect of IFNα independent of its protease activity

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Background: Combination therapy with pegylated Interferon and Ribavirin is the best treatment for patients infected with hepatitis C virus (HCV), but it is only effective in half of patients. We recently demonstrated that USP18, the ISG15-specific protease, is important to HCV responses: it is one of the 18 gene signature predictive of response to therapy (Chen *et al Gastroenterology* 2005, 2010), and knockdown of USP18 increases the anti-HCV effect of IFNα (Randall *et al Gastroenterology* 2006). In this study we investigated how USP18 protease activity modulates HCV replication with and without IFNα.
Methods: USP18 wild type (wt) and a protease-inactive mutant (USP18 C64S, mUSP18) expression constructs were cloned with an N-terminal GFP tag. Enzymatic activity of the expressed USP18 was confirmed by co-transfecting wtUSP18 or mUSP18 with plasmid DNA expressing ISG15-GST fusion protein. The effect of over-expression of wtUSP18 or mUSP18 on HCV RNA replication/viral particle secretion with or without IFNα was tested in the J6/JFH1 infectious culture system.
Results: Over-expression of wtUSP18 in Huh7.5 cells led to decreased ISGylation in the presence of IFNα, an effect not seen with overexpression of mUSP18. Overexpression of both wtUSP18 and mUSP18 increased baseline HCV RNA replication and production of infectious virus by 4–5 fold; overexpression of both also blunted the anti-HCV effect of IFNα. Neither wtUSP18 nor mUSP18 inhibited the expression of common ISGs (MxA, ISG15, OAS2, Viperin) after exposure of Huh7.5 cells to IFNα.
Conclusions: USP18 modulates HCV replication and the anti-HCV activity of IFNα independent of its protease activity and without disrupting IFNα signaling. These studies reveal that increased USP18 expression may be one way that HCV shelters itself from the host response, and should be considered a target for new anti-HCV therapies.

OL-001 Association study of genetic variation in IL28B with the hepatitis C treatment-induced viral clearance in Chinese Han population

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Background: Genome-wide association studies have recently confirmed the rs12979860 variation in IL28B is associated with the response to chronic hepatitis C (HCV) treatment. The aim of this study is to investigate whether the rs12979860 variation could be used as a predictive marker for end-of-treatment response (ETR) or sustained virological response (SVR) in Chinese Han population.
Methods: Totally, 259 HCV infected individuals were detected the rs12979860 genotypes by DNA sequencing. Among them, 120 patients with complete pegylated interferon Alfa and ribavirin combination therapy and 92 patients followed for 24 weeks after the cessation of treatment were divided into different groups according to outcomes of treatment.
Results: The rs12979860 CC genotype was the main genotype in Chinese Han patients (87.64%, 227/259) and only one TT genotype was found in this cohort of patients. The patients with rs12979860 CC genotype got higher rates of ETR ($P = 0.0044$) and SVR ($P = 0.0046$) than the patients with N-CC (CT, TT) genotypes. In multiple logistic-regression models, the rs12979860 variation was associated with a more substantial difference in rates of achieving ETR (OR: 8.983, CI: 2.173–37.145, $P = 0.0024$) and SVR (OR: 24.298, CI: 2.272–259.901, $P = 0.0083$) than the other factors, including sex, age, HCV genotypes and baseline viral load.
Conclusion: This study demonstrated that the rs12979860 variation in IL28B could be as a predictor for ETR and SVR in Chinese Han patients with HCV infection.

OL-002 Effect of high-dose ribavirin (RBV), Alinia (Nitazoxanide) and pegylated interferon (PegIFN) alfa-2a in attaining sustained virologic response (SVR) in treatment of chronic hepatitis C (ERAIS-C Trial) in naïve genotype 1 patients

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Purpose: PegIFN and Ribavirin (RBV) remain the backbone of therapy of chronic hepatitis C and achieve a sustained virologic response (SVR) rate of ~50% globally