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Hepatitis C virus quasispecies evolution during pregnancy and between consecutive pregnancies: influence of maternal immune responses

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Background

Hepatitis C virus (HCV) can be transmitted from mother-to-child during pregnancy and childbirth. Most importantly, the rate of vertical HCV transmission is increased four-fold in the presence of maternal coinfection with human immunodeficiency virus type 1 (HIV-1). To gain insight into the evolution of HCV disease during pregnancy and to better understand the influence of HIV-1 coinfection, HCV quasispecies composition was characterized longitudinally in a group of 17 pregnant women infected with HCV, including 13 subjects coinfected with HIV-1, 4 of whom were followed during 2 consecutive pregnancies.

Materials and methods

HCV RNA was extracted from serum and E2 hypervariable region 1 (HVR1) and flanking regions (positions 1278-1889) were amplified by RT-PCR. Amplicons were cloned and plasmid DNA from transformants was sequenced unidirectionally. Sequences were aligned using Clustal X. A mean of 18.8 cDNA clones of HVR1 were analyzed per time point (1,337 clones representing 1,101 non redundant sequences). Mean genetic distance (p distance) and its standard deviation were calculated using MEGA2.1. dN/dS ratios were computed according to the Nei-Gojobori method. Normalized Shannon entropy (Sn) was used to account for the frequency of each different variant in the quasispecies. Diversification of viral variants was assessed using phylogenetic reconstructions built according to the neighbour-joining method and the Kimura two-parameter model.

Results

Median aspartate aminotransferase and HCV RNA levels were higher in coinfected subjects throughout pregnancy, with 3d trimester HCV RNA levels significantly higher than those observed in subjects infected with HCV alone (p=0.0283, Mann-Whitney U test). Quasispecies complexity based on numbers of HVR1 variants or Shannon entropy was higher in subjects treated with and responding to antiretroviral therapy (treated-responders; n=11) than in untreated-nonresponders (n=6) or subjects infected with HCV alone (n=4) at all time points examined. Analysis of dN/dS ratios revealed that intrahost selective pressure was consistently larger in treated-responders than in HCV-only subjects, and always higher in HCV-only than in untreated-nonresponders. Finally, the level of diversification of HVR1 observed between consecutive pregnancies was incompatible with linear genetic drift during the inter pregnancy interval.

Conclusion

Overall, these results indicate that: a) coinfection with HIV-1 leads to reduced immune pressure on HVR1; b) this immunosuppressive effect is overturned by antiretroviral treatment; and c) pathological events observed in HCV-infected women in late pregnancy are immune-mediated. This study will lead to a better understanding of therapeutic and immune factors that influence viral evolution and the clinical outcome of hepatitis C during pregnancy.