Evolution of Hepatitis C Virus Points to Postpartum Recovery of CD8+ T-cell Selection Pressure

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Background

CD8+ T cells may transiently suppress viral replication in acute persisting hepatitis C virus (HCV) infections, but eventually lose control due to T cell exhaustion or selection of viral variants with escape mutations. With the failure of cellular immunity, high-level viremia is a hallmark of chronic infection.

Following pregnancy however, some chronically infected women experience a substantial drop in viremia.

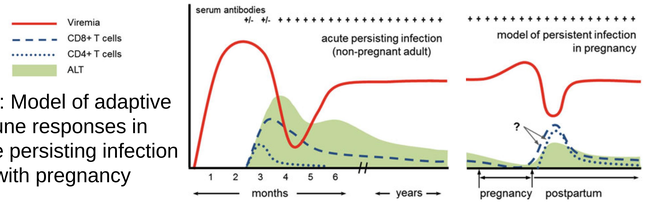


Fig 1: Model of adaptive immune responses in acute persisting infection and with pregnancy

Hypothesis

Postpartum control of viral replication is due to recovery of the HCV-specific CD8 T cell response and will thus be associated with selection of de novo escape mutations as seen in acute persisting infection.

Methods

HCV genomic evolution was compared in 8 women with different patterns of postpartum viral replication. Viral sequence data were obtained in the 3rd trimester or perinatal period (T3), 3 months postpartum (3P), and 12-24 months postpartum follow-up (FU) by Illumina or clonal Sanger sequencing of PCR amplicons spanning the HCV coding region. Analysis focused on nonstructural region to limit confounding effects of antibody pressure.

Comparison:

- Subjects were categorized based on change in HCV-RNA level from (T3) to 3P: elite controllers (>2 $\log_{10}$ drop) and noncontrollers (stable viral load)
- Nucleic acid changes were tabulated if frequency <20% at baseline and >80% of variants at follow-up. Non-synonymous changes were compared to genotype consensus sequence and assessed for location with described and predicted class I epitopes.

Cohort included:

- 4 women with viral control
- 4 women without viral control

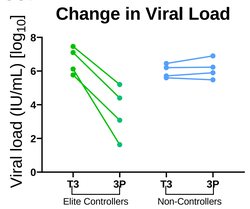


Fig 2: Viral load changes between T3 and 3P

Results

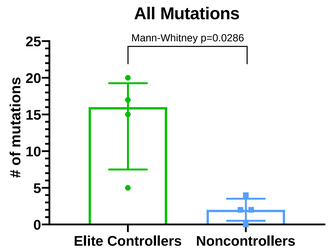


Figure 3: Comparing total mutations between T3 and FU

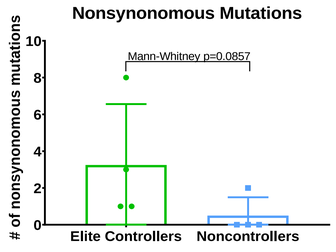
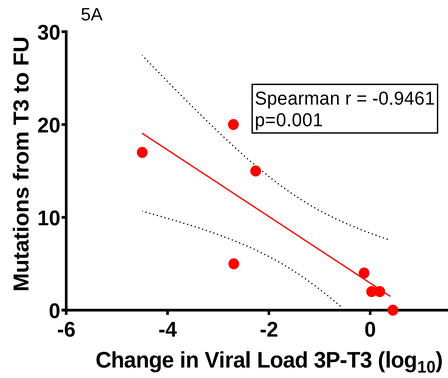


Figure 4: Non-synonymous mutations between T3 and FU



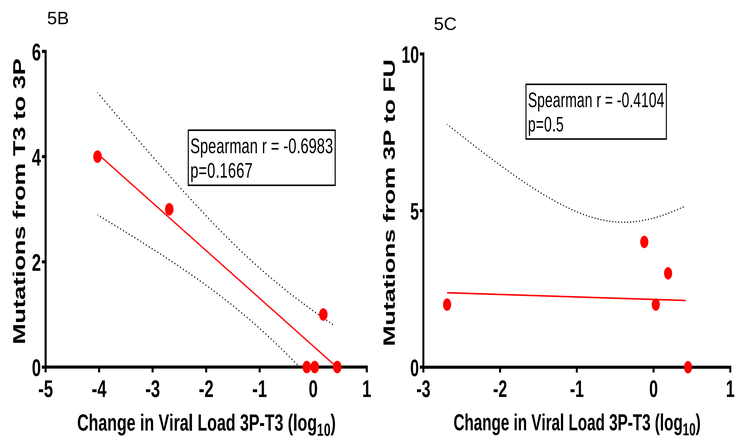
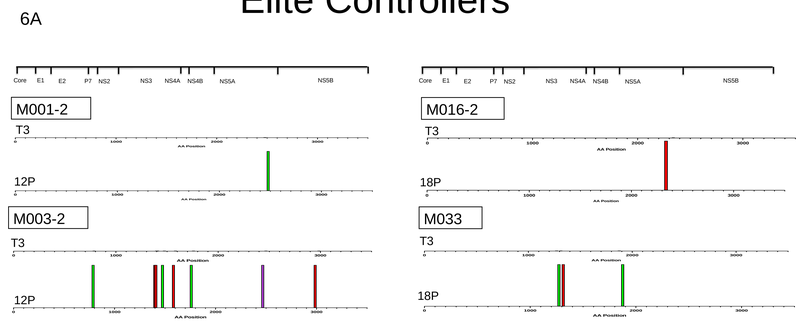


Fig 5A, 5B, 5C: Correlation of mutations with degree of viral control
A: All mutations from 3rd trimester to follow-up
B: All mutations from 3rd trimester to 3 months postpartum
C: All mutations from 3 months postpartum to follow-up

Elite Controllers



Green: toward consensus
Purple: tangential to consensus
Red: away from consensus

Noncontrollers

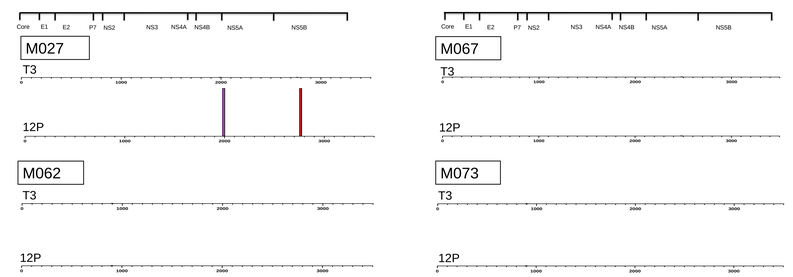


Fig 6: Visual representation of non-synonymous viral evolution after pregnancy in elite controllers (A) and noncontrollers (B) comparing 3rd trimester sequence to follow-up.

Conclusions

- Significantly more viral mutations emerged in elite controllers after pregnancy compared to non-controllers (p=0.0286), with a similar trend noted when limited to nonsynonymous mutations (p=0.0857)
- The number of mutations accumulated at follow-up correlated with degree of viral control. These changes may have been enriched in the early postpartum period among women with viral control.
- Most nonsynonymous mutations occurred in predicted class I epitopes
- Together, these findings suggest that re-exertion of HCV-specific CD8 T cell pressure may contribute to the unique control of HCV observed in some women after childbirth

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