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Differential expression/stability of core protein during HCV infection and its effect on viral life cycle

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HCV core protein plays a critical role in viral assembly as a structural component as well as a regulator of assembly site formation. Core recruits replication complexes and envelope glycoproteins to the vicinity of cytosolic lipid droplets.

In current study, we observed a differential core protein expression/stability during infectious HCV life cycle. We analyzed the expression kinetics of HCV proteins in a single viral cycle assay using a CD81-negative Huh-7 derivative cell line. It was observed that most viral proteins accumulated with a half maximal value at 25 to 27 hours post-electroporation in this system. In contrast, the half maximal accumulation of core was reached at 33 hours post-electroporation, indicating a 6-to-8-hour delay in core expression, compared to other HCV proteins. The delay in core expression was confirmed in infected Huh-7 cells using an immunofluorescence-based assay.

Our results showed an increase in core expression during late step of the viral life cycle. core was found to turn over with a half-life of approximately 90 minutes when measured at early time points of HCV infection, or in heterologous expression systems. Strikingly, there was a ten-fold increase of core half-life over the course of infection, whereas other viral proteins half-lives were not increased by more than two times.

As core protein stabilized itself during viral life cycle, to check the effect of this differential core turnover during viral life cycle, core protein was expressed at different concentration and viral replication was quantified. Core protein down regulates the viral replication in concentration/stability dependent manner. As core recruits replication complex on lipid droplets (LDs) for viral assembly, the effect of differential core stability on viral assembly was observed by expressing core in stable cell line expressing sub-genomic replicon for different time points. Our results showed that core protein at later time points after stabilized by itself, more efficiently recruits replication complex to LDs, most probable viral assembly sites.

Altogether, these results indicate that core is an unstable protein, which is stabilized when expressed at higher expression levels. In the course of HCV infection, this stabilization down regulate the HCV replication, and recruits HCV replication complex more efficiently on LDs, and shift the viral life cycle from replication to assembly. This delayed core expression may constitute a mechanism participating in the regulation of the HCV life cycle.

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