Functional study of hepatitis C virus glycoprotein E1

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By being part of the viral particle, HCV envelope glycoproteins play an essential role in virion morphogenesis as well as in HCV entry into liver cells. These two steps necessitate timely and coordinated control of HCV glycoprotein functions. Until recently, research on HCV envelope glycoproteins has been mainly focused on E2 because it is the receptor-binding protein, it is also the major target of neutralizing antibodies and it was postulated to be the fusion. However, the recent publication of the structure of E2 does not show the presence of a fusion peptide and its structure does not fit with what one would expect for a fusion protein, suggesting that E1 alone or in association with E2 might be responsible for the fusion step. Interestingly, several studies characterizing novel inhibitors of late steps of HCV entry have shown that some resistant mutations can be found in E1, re-enforcing the hypothesis that this protein plays a major role during the fusion process. Furthermore, we have also recently shown that E1 plays a role in modulating the exposure of the CD81-binding region on E2. Together, these observations indicate that E1 plays a more important role than previously thought in the HCV life cycle. It is therefore essential to better understand how E1 plays an active role in HCV entry and assembly. The objective of this proposal is therefore to investigate the functional role of HCV glycoprotein E1 by site-directed mutagenesis of conserved region in the context of an infectious clone. This will be performed in the context of the current knowledge on structural data already accumulated on this envelope glycoprotein. This study will provide the framework for a better understanding of the functional cooperativity between HCV envelope glycoproteins E1 and E2. Furthermore, it could also be helpful for the design of a vaccine candidate aiming at inducing a strong neutralizing antibody response.

Keywords: hepatitis C virus; glycoprotein; envelope proteins; viral entry; viral assembly