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Abstract
Summary

Recent data suggest that a strong early broad neutralizing antibody response may contribute to control of hepatitis C virus in the acute phase of infection. However, the majority of individuals fails to clear hepatitis C virus during the first months after contamination and develops chronic infection despite the presence of anti-HCV antibodies. A prerequisite of the understanding of the mechanisms of viral escape from antibody-mediated neutralization has been the identification of various host entry factors mediating the first steps of viral infection: binding and entry of HCV is believed to be a multi-step process involving HCV envelope glycoproteins E1 and E2 as well as several host cell surface molecules such as CD81, scavenger receptor class B type I (SR-BI), members of the claudin family and occludin. In this report, Grove et al. (J Virol 82, 12020-9 (2008)) describe a single mutation in the HCV envelope glycoprotein E2 that alters glycoprotein structure thereby modulating viral interaction with SR-BI and CD81 and increasing sensitivity to neutralizing antibodies. The results of this study highlight the importance of the characterization of the interplay between HCV particles and host cell factors for the understanding of virus neutralization by host immune responses and pathogenesis of HCV infection.

Author Keywords Hepatitis C virus ; adaptive mutation ; viral entry ; neutralizing antibodies

In this article, the recent publication by Grove et al. [1] will be reviewed. The results of this study highlight the importance of the characterization of the interplay between hepatitis C virus (HCV) particles and host cell factors for understanding viral neutralization by host immune responses.

HCV infection is a major cause of liver disease world-wide. More than 170 million invididuals suffer from chronic HCV infection which may progress to liver cirrhosis and hepatocellular carcinoma [2]. A vaccine is not available and current treatment based on interferon-alfa and ribavirin is limited by resistance, toxicity and high costs [3]. Spontaneous viral clearance occurs only in a minority of acutely infected individuals. Resolution of infection appears to require rapid, vigourous and multi-specific antiviral host immune responses [4 –7]. However, HCV has evolved mechanism(s) that counteract these responses during both the acute and the chronic phase of infection [7 –9]. Thus, in most of the cases, the immune system fails to eliminate HCV during the first months after contamination and HCV infection persists for lifetime despite the presence of antibodies targeting viral proteins. Due to its error-prone viral replicase, HCV exists as a pool of constantly changing, distinct but related genomic variants (a quasispecies) in infected individuals. The immune system exerts constant pressure on the quasispecies thereby leading to the emergence of escape mutants. A detailed follow-up of a well-characterized chronic HCV patient has provided insights into the time-course of induction of neutralizing antibodies and viral escape from neutralizing responses [10]. Interestingly, throughout the course of the disease, the antibodies of this patient lagged behind the rapidly evolving viral quasispecies, i. e. they were able to neutralize HCV strains that had been circulating several months or years before but not the present or future viral variants of the patient [10 , 11]. Escape from neutralizing antibodies in this patient has been suggested to be due in part to mutations in the hypervariable region 1 (HVR1) of the HCV envelope glycoprotein E2. This very elegant study demonstrates that the host neutralizing responses are not able to control the circulating pool of viruses during chronic infection. However, the interaction of neutralizing antibody-escape variants and HCV host cell factors still remain poorly defined.

In recent years, substantial progress has been made in understanding how HCV enters into host cells and how neutralizing antibodies interfere with this process. Binding and entry of HCV is believed to be a multistep process involving HCV envelope glycoproteins E1 and E2 as well as several attachment and entry factors, such as CD81, scavenger receptor class B type I (SR-BI), members of the claudin family and occludin [12 –22]. While HCV envelope glycoprotein E2 has been shown to directly interact with CD81 and SR-BI [12 , 13], the interaction of HCV envelope glycoproteins with the other host entry factors is less well understood [17 , 19]. As the HCV envelope glycoproteins E1 and E2 interact with host cell factors and trigger the conformational changes necessary to initiate infection, they are important targets for virus neutralization. Antibodies targeting both linear and conformational epitopes of envelope glycoprotein E2 have been shown to inhibit binding, entry and fusion of HCV [23 –31]. Viral epitopes targeted by neutralizing antibodies include epitopes of the hypervariable region 1 (HVR1) region of E2 (aa 384–410) [28 , 32 , 33], epitopes adjacent to the N-terminal region of the HVR1 region (aa 408–422 and aa 412–419) [34 –36], the E2 CD81 binding regions (aa 474–494 and aa 522–551) [28 , 35 , 37 , 38] and conformational epitopes within glycoprotein E2 [39 –42]. As the HCV envelope glycoproteins are essential for viral entry and major targets for neutralizing antibodies, it is conceivable that factors that modulate interaction of HCV with host cell factors may also modulate its interaction with neutralizing antibodies. Several physiological SR-BI ligands have been shown to modulate HCV infection: while

high-density lipoproteins (HDL) have been demonstrated to increase infection of target cells with HCV, oxidized low-density lipoproteins (LDL) inhibited HCV infection in vitro [33 , 43 , 44]. Moreover, the interplay of HCV glycoproteins with HDL and SR-BI mediated protection from neutralizing antibodies present in sera of acute and chronic HCV-infected patients [33 , 45 , 46]. The HVR1 of HCV envelope glycoprotein E2, whose variability has been associated with inability to clear the virus [47], appeared to play a major role in this process [48].

While our knowledge about the molecular mechanisms of HCV entry is rapidly advancing and recent evidence suggests that neutralizing antibodies interfere with entry steps that are closely linked to the interaction of HCV with SR-BI and CD81 [11 , 31], the understanding of the interplay between host cell entry factors, HCV envelope glycoproteins and neutralizing antibodies is still only partly understood.

To address this important question, Grove et al. [1] investigated the interaction of cell culture-derived recombinant HCV (HCVcc) bearing a single cell culture adapted mutation G451R in the E2 envelope glycoprotein with two HCV host entry factors (CD81 and SR-BI) [23 , 29 , 30]. HCV G451R was first identified as a cell culture-adapted mutant which expands more rapidly in cell culture than wild-type (wt) HCV, reaches higher specific-infectivity titres and demonstrates accelerated cytopathic effects in vitro [49]. To understand the molecular mechanism of this increased viral fitness, the authors investigated the interaction of viral particles of this variant with two well characterized HCV entry factors CD81 and SR-BI. Using both a biochemical and functional approach the authors showed that this single mutation within the HCV envelope glycoprotein E2 modulates the interaction of HCV G451R with both SR-BI and CD81. In contrast to wt HCVcc, HCV G451R did neither demonstrate increased infectivity in SR-BI overexpressing cells nor increased infectivity in the presence of HDL. In addition, compared to wild-type virus this mutation appeared to be less sensitive to inhibition of infection by anti-SR-BI antibodies. The same observation was made using anti-CD81 antibodies. These data suggest that HCV G451R is less dependent on SR-BI and CD81 on the entry level. Whether this loss of SR-BI- and CD81-dependency might be compensated by a higher usage of other HCV host entry factors remains elusive. As a reduced sensitivity to inhibition of infection by anti-SR-BI and anti-CD81 antibodies may be due to an increased binding of HCV G451R to these host cell factors, the authors compared binding of wt HCV and HCV G451R to SR-BI and CD81. Whereas soluble E2 protein from wt HCV and HCV G451R bound to SR-BI-expressing CHO cells in a comparable manner, the mutant E2 protein demonstrated an enhanced binding to CD81-expressing CHO cells as well as to recombinant CD81 dimers. In addition HCV G451R showed an increased sensitivity to inhibition of infection in the presence of soluble CD81 (large extracellular loop). These data thus suggest that the single cell culture-adapted mutation G451R increases binding of HCV to CD81. Given that the interaction of HCV envelope glycoproteins with SR-BI and CD81 may be closely linked to interaction of HCV with neutralizing antibodies [31], the authors also investigated the sensitivity of HCV G451R to polyclonal antibodies derived from chronic HCV patients and well characterized monoclonal anti-envelope antibodies. Interestingly, HCV G451R demonstrated an increased sensitivity to neutralization by both polyclonal anti-HCV IgG and monoclonal anti-E2 antibody 3/11.

The association of HCV with lipoproteins might be modulated upon conformational changes of the HCV envelope and this might change the biophysical properties of HCV as well as sensitivity to neutralization. Thus the authors investigated to what extent the G451R mutation affects distribution of HCVcc in an iodixanol densitiy gradient that allows fractioning the population of HCVcc depending on their density. Subsequently, the interaction of the different HCVcc fractions with host cell entry factors and neutralizing antibodies was analyzed to determine whether the particle density influences HCV G451R interaction with SR-BI and CD81 and HCV neutralization. While no correlation between wt or mutant virus density and sensitivity to anti-SR-BI or anti-CD81 antibodies could be observed, all iodixanol fractions of HCV G451R were completely neutralized by pooled chronic HCV patient-derived IgG whereas neutralization of wt virus increased with particle density. These data suggest that in contrast to wt HCV, the efficiency of neutralizing antibodies is not affected by the presence of lipoproteins in HCVcc bearing the G451R mutation. The molecular mechanisms underlying these differences in sensitivity to neutralization remain to be defined.

Conclusions and Future Perspectives

In this report, Grove et al. demonstrate that a single cell culture-adapted mutation in HCV envelope glycoprotein E2 alters the relationship between HCV particle density and infectivity, modulates co-receptor dependence and increases virion sensitivity to CD81 mimics and neutralizing antibodies [1]. Interestingly, viral adaptation in vitro resulting in a modulation of sensitivity to soluble co-receptors and to neutralizing antibodies has also been shown for other viruses: human immunodeficiency virus 1 (HIV-1) adapts to replication in cell lines in vitro by becoming sensitive to soluble CD4 and neutralizing antibodies [50]. Moreover, human respiratory syncytial virus variants with increased infectivity titres and increased susceptibility to neutralizing antibodies upon cell culture adaptation have been described [51]. The molecular mechanisms underlying these observations are only partly understood. Such cell culture-adapted mutations may expose co-receptor epitopes on circulating viruses or stabilize a conformation of the viral envelope that is well recognized by neutralizing antibodies. This is conceivable for the mutation described herein [1] given that glycine 451 is located downstream of HVR1, an E2 region involved in interaction with SR-BI, and upstream of a CD81 binding region of E2. The characterization of viral variants and the elucidation of the interactions of such mutants with co-receptors is undoubtedly of great scientific interest and contributes to the discovery of important neutralizing epitopes that may be useful for vaccine design.

What is the impact of the identified mutation in vivo? As the majority of HCV infected patients develop chronic infection despite the presence of anti-HCV antibodies, antibody-escape mechanisms most probably operate in vivo. As HCV G451R is extremely well neutralized by anti-HCV antibodies isolated from HCV infected patients, one may speculate that if such a G451R mutation arises in vivo, it will be eliminated very quickly from the circulation as neutralizing antibodies would probably be a counter-selection pressure against this adaptation. In vivo, HCV tends to adapt to its host by escaping from neutralizing antibodies. Indeed, Zhong et al. demonstrated that only one out of 502 sequences bearing an arginine instead of glycine in the HCV envelope glycoprotein E2 at position 451 was found [49] suggesting that glycine 451 is highly conserved among HCV genotypes.

Characterizing the interaction of an in vivo escape mutant with host cell factors and neutralizing antibodies, a recent study demonstrated that a HCV variant isolated from a well characterized patient with chronic HCV infection, and located outside the CD81 binding region of E2, was characterized by a decreased infectivity and decreased sensitivity to neutralization [11]. These results suggest that both in vitro and in vivo adaptive mutations may arise that are located outside the known CD81 binding regions. However in contrast to the in cell culture-derived mutation described by Grove et al. [1] that was characterized by increased viral fitness due to enhanced binding to CD81, the patient-derived variant described by Keck et al. [11] compromised viral fitness by decreasing binding to CD81. Moreover, while the cell culture-derived variant was more efficiently neutralized than wt HCV, the patient-derived variant was able to escape host neutralizing antibody responses. Evasion from antibody-mediated neutralization through decreased receptor binding has also been reported for other viruses such as HIV-1 [52]. Furthermore, a recent study described an in vitro escape mutation HCV N415Y that lowered viral fitness without affecting binding to CD81 [53] suggesting that mutations modulating interaction with host cell factors other than CD81 may also contribute to escape of HCV from neutralizing antibodies. Taken together, these studies show that mutations within the HCV envelope glycoproteins modulate viral entry and neutralization by anti-HCV antibodies.

Another interesting finding of the study from Grove et al. is the observation that the sensitivity to neutralization by anti-HCV antibodies increased with particle density for JFH-1 wt, suggesting that lipoproteins interfere with HCVcc neutralization. This is in line with previous studies describing a tight interplay between HDL, SR-BI and HCV promoting both HCV entry into host cells and escape from neutralizing antibodies [33 , 45 , 46]. In contrast to wt HCV, no differences in the neutralization of HCV G451R gradient fractions were observed [1]. Surprisingly, all fractions were equally well neutralized, suggesting that the efficiency of neutralizing antibodies is not affected by the presence of lipoproteins in HCVcc bearing the G451R mutation. Further studies are needed to address the mechanisms of this finding that may have an important impact for vaccine design.

Taken together, these observations highlight the importance of the investigation of the relationship between HCV envelope glycoproteins, lipoproteins and host cell entry factors for better understanding the mechanisms of HCV entry and neutralization. Moreover, the results of the study suggest that for the assessment of neutralization studies investigating novel immunopreventive or therapeutic strategies, ‘early passage’ or non-adapted HCV strains rather than cell culture-adapted HCV variants should be used. The use of ‘early passage’ or non-adapted HCV strains for neutralization assays will avoid to overestimate the magnitude of neutralization compared to neutralization occurring in vivo as shown for HIV [54].

Executive Summary

Objectives of this study

- To investigate whether the cell-culture adaptive mutation G451R affects recombinant hepatitis C virus (HCV) JFH-1 interaction with the HCV entry factor scavenger receptor class B type I (SR-BI).
- To determine whether the adaptive mutation G451R affects recombinant hepatitis C virus (HCV) JFH-1 interaction with the HCV entry factor CD81.
- To study the relationship between viral particle density and SR-BI and CD81 receptor-dependent infection.
- To investigate the effects of the adaptive mutation G451R on viral particle sensitivity to neutralizing antibodies (nAbs).

Methods

- Parental human hepatoma Huh7.5 cells and cells overexpressing SR-BI were infected with JFH-1 wt and G451R.
- Infectivity was determined by NS5A immunostaining and quantified by enumerating the total number of infected cells per well.
- For neutralization and receptor blocking experiments, virus or cells were preincubated with antibodies prior to infection.
- For particle density studies, JFH-1 and G451R were purified using iodixanol gradients.
- Binding of soluble E2 to SR-BI and CD81 was assessed using transfected CHO cells and flow cytometry.

JFH-1 G451R has a reduced dependence on SR-BI

- Overexpression of SR-BI enhanced infectivity of JFH-1 wt 4 to 8-fold but not infectivity of JFH-1 G451R
- JFH-1 G451R was less sensitive to inhibition of entry by a neutralizing polyclonal anti- SR-BI serum than JFH-1 wt.
- JFH-1 G451R infectivity was unaltered by HDL wheras HDL promoted JFH-1 wt infectivity by 2-fold.

JFH-1 G451R has an increased sensitivity to neutralization by soluble CD81

- JFH-1 G451R was less sensitive to inhibition of entry by two neutralizing anti-CD81 mAbs than JFH-1 wt.
- JFH-1 G451R demonstrated increased sensitivity to neutralization by human CD81 large extracellular loop.

JFH-1 G451R sE2 demonstrates increased binding to CD81

- Soluble E2 protein from JFH-1 wt and G451R bound to CHO-SR-BI cells with comparable staining intensities.
- The mutant G451R soluble E2 protein showed a 50%-enhanced binding to CHO-CD81 as compared to the wt protein.
- CD81 dimers bound approximately 3-fold more JFH-1 G451R than wt soluble E2 protein.

Relationship between JFH-1 and G451R particle density, infectivity, and co-receptor interactions

- JFH-1 G451R appears to increase the infectivity of higher-density particles while perturbing the infectivity of lower-density particles.
- There was no correlation between wt or mutant virus density and sensitivity to SR-BI and CD81 antibodies.

JFH-1 G451R sE2 demonstrates an increased sensitivity to nAbs

- JFH-1 G451R demonstrated a 50-fold increased sensitivity to neutralization by polyclonal IgG derived from chronic HCV patients.
- JFH-1 G451R demonstrated an increased sensitivity to neutralization by mAb 3/11 targeting E2 amino acids 412 to 423.
- In contrast to JFH-1 wt, all iodixanol gradient fractions were completely neutralized by pooled chronic HCV patient-derived IgG.

Conclusions

- Mutation of amino acid 451 in HCV envelope glycoprotein E2 alters the relationship between particle density and infectivity, modulates co-receptor dependence, and increases virion sensitivity to CD81 mimics and neutralizing antibodies.

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Footnotes:

Evaluation of: Grove J, Nielsen S, Zhong J, Bassendine MF, Drummer HE, Balfe P and McKeating J: Identification of a residue in hepatitis C virus E2 glycoprotein that determines scavenger receptor BI and CD81 receptor dependency and sensitivity to neutralizing antibodies. J Virol 82 (24), 12020-12029 (2008)

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