Studying the Conformational Dynamics of the Hepatitis C Virus E1E2 Complex through a Computational Lens

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BACKGROUNDS

Hepatitis C Virus (HCV) is a virus that is the cause of hepatitis C – an infection that affects over 58 million people across the world[1] and is the cause of numerous negative outcomes including cirrhosis, chronic liver disease and hepatocellular carcinoma. The major pharmaceutical point of interest on the surface of HCV is the E1E2 heterodimer complex – which is important in it being the sole membrane-bound protein involved in the pathogenesis of HCV, making it a key target for pharmaceutical applications. However, the conformational structure of E1E2 is obscured due to various reasons including the sequence diversity in the complex across HCV strains[1]. As a result, we seek to obtain critical information on the structure of E1E2 and point out points of interest on the structure through a computational lens, potentially shedding light on aspects of the structure that are deemed useful for vaccine development

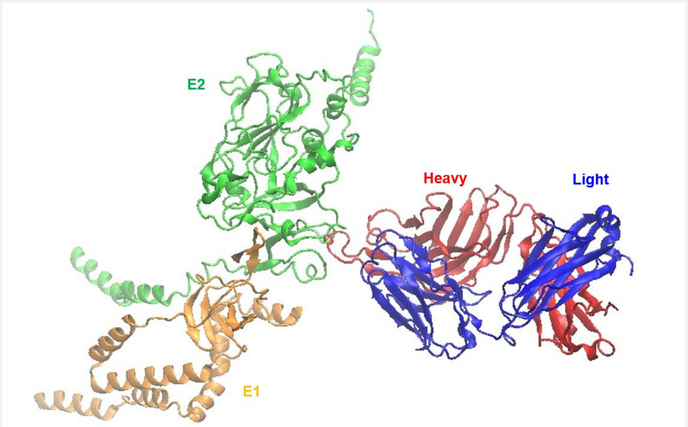

Figure 1. E1E2 complex with mAb AR4A shown. The different domains of the protein and the antibody are labelled in different colours as shown here. The systems were created through obtaining the E1E2 complex through Cryo-EM and then binding the structure with the antibody to then simulate the system

METHODS

- Used a recent Cryo-EM structure of E1E2 to generate the wild-type system
- Used the wild-type (WT) system to then generate various mutant systems of E1E2
- Bound the E1E2 systems with the AR4A monoclonal antibody (mAb) which was done through molecular dynamics (MD) simulations
- Estimated binding energies between E1E2 and AR4A through MMPBSA calculations
- MMPBSA calculations are then optimized to reflect experimental results
- Breaking down binding affinities to residue contributions
- Identification of critical residues of the E1E2 complex for vaccine development

RESULTS

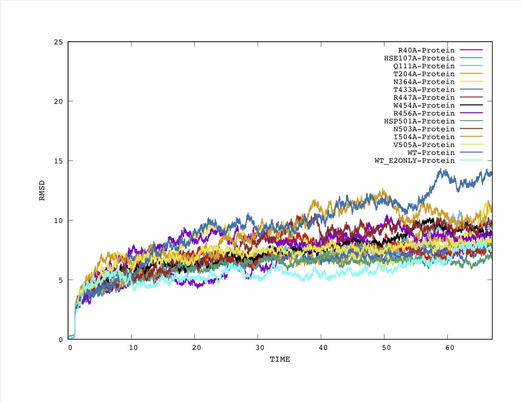

Figure 2. RMSD values for receptor backbone for 65 ns for WT and mutated systems. Variable stability was seen after the 65 ns for the WT, but mutated systems

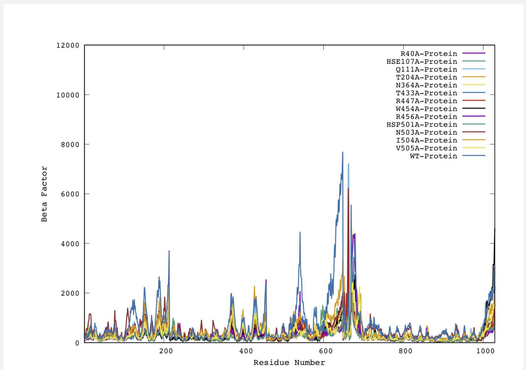

Figure 3. Beta-factor values for the various E1E2-AR4A systems. A significantly high spike in values occur around residues 600-700 for all of the systems

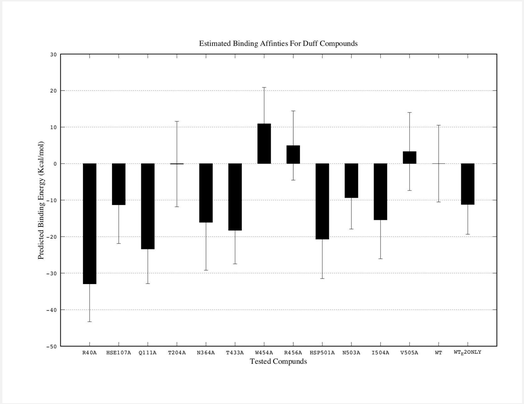

Figure 4. Binding affinities of the mutated systems compared to the WT. Values are compared to experimental results. Higher values indicate weaker binding and lower values indicate stronger binding.

CONCLUSIONS

- Comprehension of the conformational dynamics and implications of mutations on E1E2 is needed for vaccine design against HCV.
- Further configuration of binding affinity calculations should be made to conform with experimental results
- Viewing critical residues and regions can guide the rationale design of anti-HCV vaccines in the future

REFERENCES

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2. de la Peña AT, Sliepen K, Eshun-Wilson L, Newby M, Allen JD, Koekkoek S, Chumbe A, Crispin M, Schinkel J, Lander GC, Sanders RW, Ward AB**: Structure of the hepatitis C virus E1E2 glycoprotein complex**. *Nature* 2022;378:263–9

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