Norovirus: Pathogenic Shape-Shifter

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Abstract:

Norovirus is a highly infectious pathogen with poorly understood molecular virology. In which conformational flexibility in the P domain of the major structural protein VP1 plays an increasingly important role. Enhancing cellular attachment, cellular entry, and immunological escape.

Introduction:

- Norovirus is an enteric pathogen that in infects intestinal epithelial cells (IECs) and intestinal immune cells, primarily through the fecal-oral route.
- 677 million cases of gastroenteritis and 214,000 deaths are attributed to norovirus infection annually (1).
- More vulnerable demographics experience more severe outcomes: children <5 and adults >65 years of age (1).
- New variants emerge every 2-4 years that cause genotype specific immunity, allowing serial infections with multiple genotypes (1).
- There are currently no specific antiviral therapeutics or vaccines. Due in part to a lack of understanding of the molecular viral life cycle and infection.
- In particular, various conformational changes in the capsid protein VP1, specifically the P domain.
- The aim of this project was to determine the significance of conformational variation in the P domain and the cofactors that mediate it.
- Due to difficulty in culturing human norovirus (HNV), much of the research into norovirus uses murine norovirus (MNV) as a surrogate model.

Acknowledgments:

I would like to thank Dr. Morgan Herod for his invaluable academic and personal support throughout this project.

Key References:

(1) Vos, T et al. *Lancet*. **386**(9995), pp.743–800.
(2) Sherman, M.B et al. *Journal of virology*. **93**(19).
(3) Creutznacher, R et al. *BioRxiv*.
(4) Kilic, T et al. *Journal of virology*. **93**(2).
(5) Smith, H.Q. and Smith, T.J. *Viruses* **11**(3), p.236.

Dynamic capsid conformations:

Figure 1a: Schematic structure of norovirus

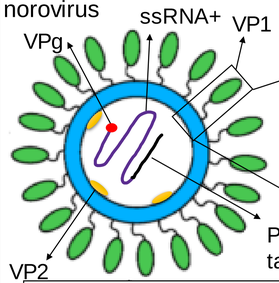


Figure 1b: Schematic of capsid protein VP1 dimer structure

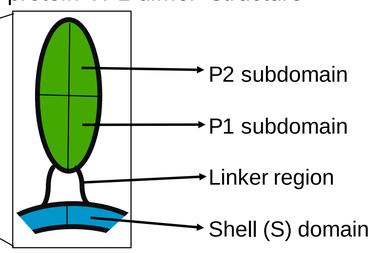


Figure 2: MNV P domain in the rising and open conformation

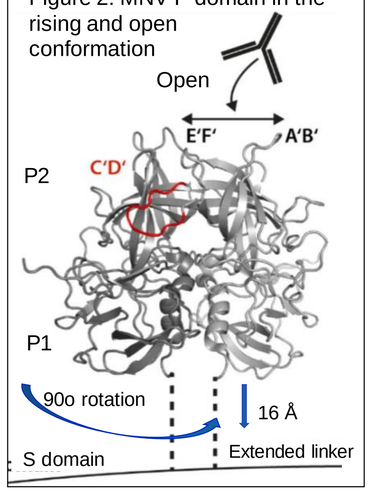
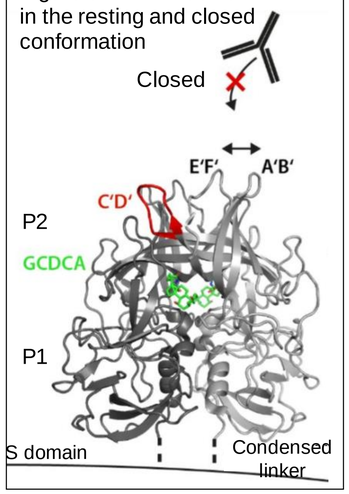


Figure 3: MNV P domain in the resting and closed conformation

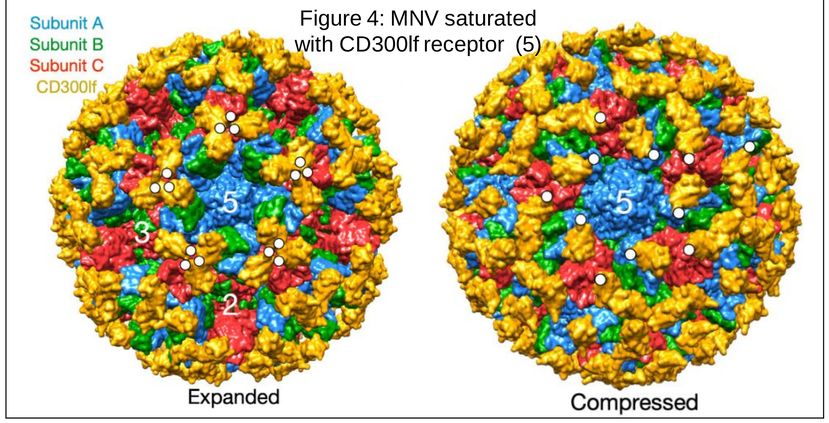


- The norovirus capsid is primarily formed of structural protein VP1, that is divided into the S and P domains. The S domain forms a shell around the RNA genome while the P domains of 2 VP1 proteins dimerise (fig 1b).
- In the apo form the P domain dimer 'floats' 16 Å off the shell, in what is termed the '**raised**' conformation (fig 1 and 2). Binding of the bile salt glycochenodeoxycholic acid (GCDCA) to the P domain dimer induces condensation of the linker region by an unidentified mechanism. A subsequent 90° counterclockwise rotation and translocation of the P domain onto the shell, produces what is termed the '**resting**' conformation (fig 3) (2).
- The C'D' loop partially covers the GCDCA binding pocket. Upon GCDCA binding, the C'D' loop is displaced and moves upward, pushing the E'F' and A'B' loops together. Changing them from an **open** (fig 2) to **closed** (fig 3) conformation (3).

Implications of a dynamic capsid:

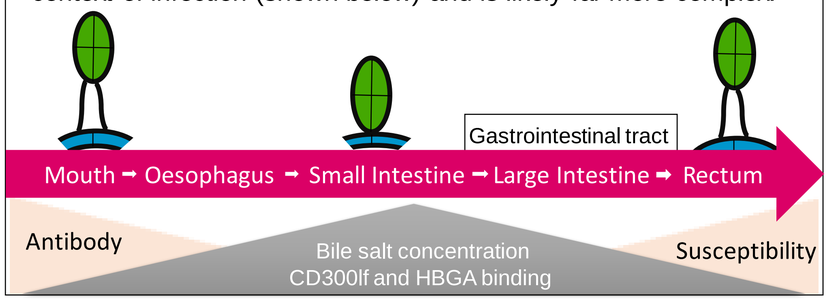
CD300lf: P domain rotation in the resting orientation increases the distance between (fig 4) and maximum number of CD300lf (MNV receptor) binding sites (located at P2 subdomain tip). This raises the avidity for CD300lf, enhancing cellular infectivity (2).
HBGAs: GCDCA binding repositions Asp375 in the HBGA (cellular attachment factor) binding pocket in HNV. The otherwise nonbinding genotype GII.1 can then bind HBGA, other genotypes interactions can also be enhanced. In both cases permissive cell adsorption is increased (4) .
Antibodies: Some antigenic sites present in the rising conformation are not in the resting, making the related antibodies non-neutralising (2). Between the E'F' and A'B' loops lies a hydrophobic patch that makes significant contacts with neutralising antibodies 2D3 and 4F9. This is inaccessible in the closed conformation (fig 3). Which can be allosterically induced by both escape mutants or GCDCA (3).

Figure 4: MNV saturated with CD300lf receptor (5)



Conclusion:

Norovirus' dynamic capsid plays a significant role in ligand binding and antibody evasion. This is only partially understood in the wider context of infection (shown below) and is likely far more complex.



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