Natural Variation in Norovirus Strains Impacts Breadth of Virus-Ligand Interactions

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Abstract

Globally, diarrheal diseases account for 1 in 9 deaths in young children, with human norovirus being the leading cause of viral acute gastroenteritis outbreaks in the United States[1,2]. Comprising of nearly 50 various genotypes, noroviruses have evolved with extensive genetic diversity, broadening their range of susceptible human populations. Human norovirus infection is mediated by host expression of histoblood group antigen ligands within their gastrointestinal system. These virus-ligand interactions correlate with populations susceptible to infection[3,4]. To understand how natural variation within a single genotype of human norovirus mediates ligand recognition, Virus Like Particles (VLPs) of two GII.12 isolated strains (GII.12A and GII.12B) exhibiting 5 amino acid differences were compared. After differential ligand binding was recognized between the two strains, it was observed that natural variation at residue 392 on the VLP potentially could cause differential ligand B binding stability due to steric hindrance in a known ligand binding pocket at residue 436 on the VLP[5]. To test this hypothesis, a point mutation was introduced by swapping residue 392 in both GII.12 strains. Carbohydrate binding results indicated that a singular amino acid change between the GII.12A and GII.12B isolates caused a distinct switch in B-ligand recognition, indicating that residue 392 was highly involved in B-ligand recognition. Furthermore, it was hypothesized that environmental factors such as

bile, which is naturally present within the gastrointestinal tract upon infection, could impact ligand recognition by the GII.12 strains. Carbohydrate binding results demonstrated that host co-factors like bile, coupled with natural variation within the GII.12 strain, allowed for varied affinity to ligand B, and improved affinity to ligand A. The data indicates that the GII.12 norovirus utilizes both natural variation in carbohydrate binding regions on its capsid, as well as environmental host cofactors like bile, to allow for a broader range of human ligand recognition, thus expanding its potential pool of susceptible host populations.