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Conformational changes in human Norovirus polymerase

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Human Noroviruses (NV) belong in the Caliciviridae family and are a major cause of gastroenteritis outbreaks throughout the world. Crystal structures of the RNA-dependent RNA polymerase from the human Norovirus have been determined in over ten different crystal forms in the presence and absence of divalent metal cations, nucleoside triphosphates, inhibitors and primer-template duplex RNA. These structures show how the polymerase enzyme can adopt a range of conformations in which the thumb, fingers and palm domains change orientations depending on the step of the enzymatic cycle trapped in different crystal forms. We discuss how the evidence from crystallographic and biochemical experiments combine to better understand how viral RNA polymerase enzymes from human Norovirus and related positive-strand RNA viruses can adopt a range of conformational states to facilitate RNA binding, NTP binding, catalysis, RNA translocation and pyrophosphate release. The detailed structural and mechanistic understanding of these conformational changes is important for providing a sound basis for understanding viral replication in general, as well as for the design of novel inhibitors capable of trapping the enzyme in specific conformational states.

[1] Zamyatkin, D.F. et al. *J. Biol. Chem.* 283:7705-7712, 2008., [2] Zamyatkin, D.F. et al. *J. Mol. Biol.* 390:10-16, 2009., [3] Ng, K.K.S. and F. Parra. *Caliciviruses: molecular and cellular virology.* Horizon Press. 2010.

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