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Structural analysis of murine norovirus RNA-dependent RNA polymerase complexed with VPg

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Norovirus is the leading cause of acute nonbacterial gastroenteritis and replicates through de novo or viral protein genome-linked (VPg)-primed RNA synthesis by RNA-dependent RNA polymerase (RdRp). To understand the interaction of RdRp with VPg in norovirus replication, we determined the crystal structure of the RdRp-VPg(1-73) complex derived from murine norovirus (MNV). VPg binds mainly to the base of the palm domain of RdRp with minor interactions with the tip of the fingers domain. Electron microscopic and biochemical studies demonstrated that it mediated the formation of high-order multimers or tubular fibrils of RdRp in the presence of RNA, which resulted in significantly increased polymerase activity. The RdRp mutants at the interaction interface were found to bind to VPg much weaker than the native, resulting in little multimer formation, and the viral replication in the replicon system was significantly inhibited. The interaction of RdRp with VPg may play a crucial role in the organization of RdRp complexes and facilitate the enhanced activity of RNA synthesis and consequent viral replication, which provides a new target for controlling norovirus outbreaks.