Poster Presentation

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Structural basis for VPg-induced formation of RNA-dependent RNA polymerase multimeric complexes

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Norovirus is the leading cause of epidemic acute, nonbacterial gastroenteritis, and adopts de novo and VPg (Virion protein genome linked)-primed RNA synthesis by RNA-dependent RNA polymerase (RdRp). To understand the interaction between RdRp and VPg in replication of murine norovirus-1 (MNV-1), we determined the crystal structure of MNV-1 RdRp-VPg(1-73)-RNA complex. VPg was bound to the base of the palm domain and the tip of the fingers domain of RdRp simultaneously, but RNA template could not be modeled. The binding affinity constants (Kd) for RdRp-VPg was 3.74±1.57 nM and VPg(1-73) showed approximately 90-fold less affinity than that of full-length VPg. In addition to this multiple binding mode, VPg enhanced the interactions of RdRp hexamers, leading to the formation of high-order multimers or tubular fibrils with significantly increased polymerase activity, confirmed by electron microscopic and biochemical studies. Our data indicated that MNV-1 VPg with helical structure was bound to RdRp at multiple sites and induces RdRp multimerization in viral replication. The multimers of RdRp-VPg-RNA can provide a mechanistic understanding of viral polymerase multimeric arrays and a new tool for development of antivirals to control norovirus outbreaks. This work was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health, Welfare and Family Affairs (A085119 K.H.K), Basic Science Research Program through the National Research Foundation (NRF-2013R1A1A2064940, L.J-H), Korea University Grant (L.J-H), and the BK21 plus program of the Ministry of Education, Korea.

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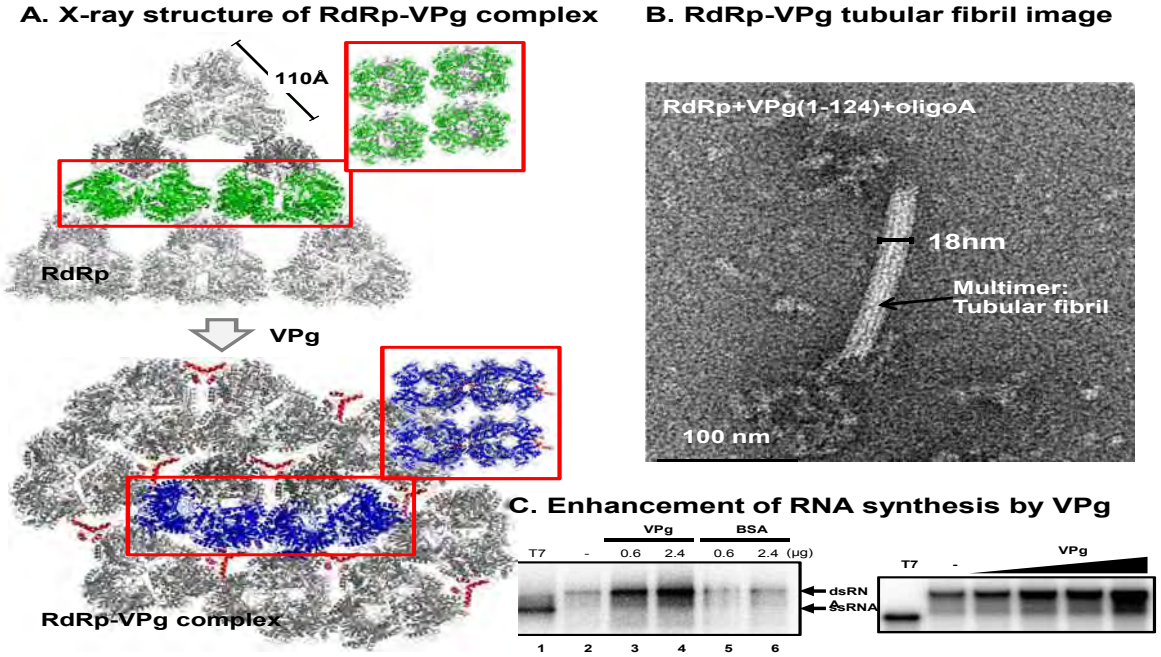

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