Structure of the human respiratory syncytial virus M2-1 protein in complex with a short positive-sense gene-end RNA

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The M2-1 protein of human respiratory syncytial virus (HRSV) is a zinc-binding transcription anti-terminator that regulates the processivity of the HRSV RNA dependent RNA polymerase (RdRP). Here, we reported a crystal structure of HRSV M2-1 bound to a short positive-sense gene-end RNA (SH7) at 2.7 Å resolution. We identified multiple critical residues of M2-1 involved in RNA interaction and examined their roles using mutagenesis and MicroScale Thermophoresis (MST) assay. We found that hydrophobic residues such as Phe23 are indispensable for M2-1 to recognize the Adenine (A) base of RNA. We also captured spontaneous binding of RNA (SH7) to the M2-1 protein in all-atom simulations using a robust Gaussian accelerated molecular dynamics (GaMD) method. Both the experiments and simulations revealed that two separate domains of M2-1 interact with RNA, suggesting that the recognition of RNA by the zinc-binding domain (ZBD) and binding of RNA by the core domain (CD) are independent of each other. Collectively, our results provided a structural basis for RNA recognition by HRSV M2-1.