proceedings

Abstract

Structure of the RSV Polymerase Complex Reveals a Tentacular Arrangement of the Viral Phosphoprotein †

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† Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 3 July 2020

Abstract: Numerous interventions are currently in the process of clinical development for respiratory syncytial virus (RSV) infection, including the use of small molecules that target viral transcription and replication. These processes are catalyzed by a complex comprising the RNA-dependent RNA polymerase (L) and the tetrameric phosphoprotein (P). The RSV P performs many functions, including the recruitment of viral proteins to the polymerase complex. Despite their critical roles in RSV transcription and replication, the structures of L and P have remained elusive, though RSV P is thought to be intrinsically disordered in solution, with the exception of its oligomerization domain. Here, we describe the 3.2 Å cryo-EM structure of RSV L bound to the tetrameric P. The structure reveals a striking tentacular arrangement of P in which each of the four monomers adopts a distinct conformation. The structure also provides a rationale for the inhibitor-escape mutants and mutations observed in live attenuated vaccine candidates. These results provide a framework for determining the molecular underpinnings of RSV replication and transcription and should facilitate the design of effective RSV inhibitors.

Keywords: RdRp; pneumovirus; electron microscopy