A STRUCTURAL AND DYNAMIC ANALYSIS OF A VIRAL PLATFORM PROTEIN

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Respiratory syncytial virus (RSV) is a highly prevalent pathogen responsible for severe lower respiratory tract infections in children. Despite longstanding research effort, there are still no vaccines nor antiviral drugs. However, the molecular mechanisms of RSV infection and replication have been unravelled step by step over the years. The latest major breakthrough was made with the cryo-EM structures of its polymerase, that gave unprecedented insight into viral RNA synthesis for RSV and cognate viruses. The polymerase is a complex formed by a large subunit and a phosphoprotein (P protein). The P protein remained largely elusive to structural elucidation, and only part of it was solved in the polymerase complex, due to its intrinsically disordered nature.

By using NMR we focused on the more flexible regions of RSV P. We combined a protein fragment approach with chemical shift, nuclear relaxation, paramagnetic relaxation and high pressure NMR measurments to investigate the degree of disorder in RSV P. We found regions with secondary structure propensity, some with high others with low propensity. These regions are in rapid conformational exchange in their free form. RSV P protein interacts with several other RSV proteins (L, N, M2-1, M) as well as cellular proteins (PP1, Hsp70). We showed that many of the transiently structured regions in RSV P are small linear motifs (SLiMs) that serve as molecular recognition elements for these protein partners. The structure of these SLiMs is stabilized in the complex form. The large amount of instrincally disordered regions affords multiple small binding sites. The quaternary structure of the tetrameric RSV P protein allows combination of the binding sites. RSV P is thus able to act as a scaffold protein that brings other proteins close into space, like in the case of RSV M2-1 and the PP1 phosphatase that only dephosphorylaytes M2-1 in the presence of P.

References: Pereira et al, J Biol Chem 2017; Richard et al, PLos Pathogens 2018; Cardone et al, IJMS 2021; Cardone et al, Biomolecules 2021.

Scheme of RSV P protein and interaction regions