MS06-P02 | STRUCTURAL BASIS FOR RNA TRANSLOCATION AND NTP HYDROLYSIS BY THE ZIKA VIRUS NS3 HELICASE

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Flaviviruses are single-stranded positive sense RNA viruses. Several members of this family, such as Dengue, Yellow Fever, and Zika viruses, are associated with important human diseases. Flaviviral non-structural protein 3 (NS3) helicase participates in RNA unwinding and capping, and is crucial for viral replication [1,2]. X-ray structures for protein complexes with a polynucleotide and/or NTP analogs have been reported for several Flaviviral NS3 helicases. However, the mechanism of coupling NTP hydrolysis with RNA translocation remains unclear.

In this study, we determined the first crystal structure for the Zika virus NS3 helicase complex with an ssRNA segment containing 5'-phosphate. Notably, the presence of the 5'-phosphate induces significant remodeling of the interactions with the 5'-nucleotide of RNA, unveiling the breadth of structural changes that can occur during RNA unwinding. Additionally, we determined the X-ray structures of the NS3 helicase in several different functional states of NTP hydrolysis, including the pre-hydrolysis, transition state and post-hydrolysis. Structural observations indicate how a catalytically important loop, that is involved in ATP hydrolysis, can mediate coupling with RNA translocation. Structural data are substantiated by NMR analysis of the NS3 helicase transition state complex, which demonstrate that the presence of RNA enhances the transition state formation. Taken together, our data clarify the mechanism for RNA unwinding that is applicable to all Flaviviridae family NS3 helicases.

[1] C. J. Neufeldt, *et al*., *Nat. Rev. Microbiol.***2018**, *16*, 125–142.
[2] V. J. Klema, *et al.*, *Viruses***2015**, *7*, 4640–4656.