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Abstract

Structural and Functional Studies of Chikungunya Virus nsP2 †

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Abstract: Chikungunya virus (CHIKV) is transmitted to humans through mosquitoes and causes Chikungunya fever. Nonstructural protein 2 (nsP2) contains an N-terminal RNA helicase with both nucleotide triphosphatase and RNA triphosphatase activities, and a C-terminal cysteine protease that is responsible for polyprotein processing. Both N-terminal RNA helicase and C-terminal cysteine protease are connected through a flexible linker. Although the structure of the C-terminal cysteine protease has been solved, the structure and the conformational arrangement of full-length nsP2 remains elusive. Here, we determined the crystal structure of the helicase part of the CHIKV nsP2 (nsP2h) bound to the conserved 3′-end of the genomic RNA and the nucleotide analogue ADP-AlF_4. The structure of this ternary complex revealed the molecular basis for viral RNA recognition and ATP hydrolysis by the nsP2h. Unique hydrophobic protein–RNA interactions play essential roles in viral RNA replication. We also determined the solution structure of full-length nsP2 using small-angle X-ray scattering (SAXS). The solution architecture of the nsP2 was modeled using the available high-resolution structures and program CORAL (complexes with random loops). The CORAL model revealed that nsP2 is partially unfolded and the N-terminal protease domain is arranged near the N-terminal domain of the helicase domain. These findings expand our knowledge of CHIKV and related alphaviruses and might also have broad implications for antiviral and vaccine developments against pathogenic alphaviruses.

Keywords: Chikungunya virus; helicase; protease