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Commentary

Biochemical and Biophysical Characterization of the RNA-Dependent RNA Polymerase from Chikungunya

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ABOUT THE STUDY

Chikungunya virus (CHIKV) is the causative agent of Chikungunya fever, an acute febrile and arthritogenic illness with no effective treatments available. With a thorough understanding of the molecular components of CHIKV replication, the development of viable treatments options could be considerably accelerated. Drug discovery, on the other hand, is hampered by our lack of understanding of their key components. The RNA-polymerase RNA-dependent (nsP4-CHIKV) enzyme is thought to be a critical component of the CHIKV replication complex and a potential target for antiviral treatment. Experimental and computational biophysical methods were used to characterise the nsP4-CHIKV in this study. A chemical known as LabMol-309 was discovered and mapped to bind to the nsp4-CHIKV active site in the search for novel anti-CHIKV compounds. Using a CHIKV replicon system and a reporter virus, the inhibitory activity of LabMol-309 was tested in cellular-based antiviral experiments. Finally, our study identifies a novel molecule as a possible antiviral drug against CHIKV infection by highlighting biophysical characteristics of nsP4-CHIKV.

Chikungunya fever is caused by the virus, which belongs to the *Togaviridae* family. The bite of infected female mosquitoes of the *Aedes* is the principal mode of transmission. After CHIKV infection, the proportion of individuals who develop clinical and debilitating symptoms is considered the highest compared to other arboviruses, with an average of 80% of symptomatic cases. The control of the mosquito vector remains the best prophylaxis since there are no licensed vaccines or efficient antivirals available. In this scenario, the infection caused by CHIKV has a high social impact and constitutes a serious public health issue.

CHIKV is a spherical, enveloped, and positive single-stranded RNA virus. As a member of the Alphavirus genus, its genome has approximately 12 kb and codes for two distinct polyproteins: structural and nonstructural. The first one is cleaved and gives rise to five structural proteins – E1, E2, E3, C and 6k – which are part of the structure and viral assembly. The envelope proteins, specially E2 and E1, are responsible for virus anchoring, receptor interaction and membrane fusion, promoting virus entry in the host cell. Envelope proteins are targets of the humoral immune response due to their position on the viral surface, and so become targets for the creation of a CHIKV vaccine.

Considering nsP4-CHIKV as a promising target, a screening of compounds was performed through the DSF technique, and a compound designated LabMol-309 was identified. This biomolecular interaction was validated through MST, resulting in an interaction at a low micromolar range. The NMR was also used to confirm the interaction of LabMol-309 and nsP4-CHIKV, demonstrated the occurrence of chemical shifts perturbations and in silico molecular dockings and molecular dynamics simulations suggested the possible binding mode of this compound and its maintenance at the active site. Finally, the inhibitory activity of LabMol-309 was evaluated in cellular-based antiviral assays using a CHIKV replicon system and a reporter virus, demonstrating the inhibitory potential of this compound.

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