Research Theme
Infection and Immunity

Research Project Title
Targeting the Chikungunya Virus Replication Process for Antiviral Therapeutics Development

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Project Description
Chikungunya virus (CHIKV) is the causative agent of the acute febrile illness called chikungunya fever (CHIKF) that often leads to painful and long lasting arthritic sequelae. Similar to Dengue virus and Zika virus, CHIKV is transmitted to humans via mosquitoes and is prevalent in tropical and subtropical countries all around the world. The spread of three viruses across the world has increased the difficulty of prevention, diagnosis and treatment of the diseases. Unfortunately, there are no vaccine or antiviral drugs to treat CHIKF to date.

Figure 1. The Alphavirus life cycle. Following the cytoplasmic delivery of the core and release of the viral genome. Two precursors of non-structural proteins (nsPs) are translated from the viral mRNA.
and cleavage of these precursors generates nsP1–nsP4. nsP1 is involved in the synthesis of the negative strand of viral RNA and has RNA capping properties, nsP2 displays RNA helicase, RNA triphosphatase and proteinase activities and is involved in the shut-off of host cell transcription, nsP3 is part of the replicase unit and nsP4 is the viral RNA polymerase. These proteins assemble to form the viral replication complex, which synthesizes a full-length negative-strand RNA intermediate. This serves as the template for the synthesis of both subgenomic (26S) and genomic (49S) RNAs. Adopted from Schwartz O. and Albert M, 2010.

An important barrier to producing an effective vaccine or antiviral drug against CHIKV as well as many infectious positive sense RNA viruses is the paucity of information about the replication complex (RC). In this proposal, we aim to determine the molecular architecture of the multimeric viral RNA replication complex and reveal the essential protein-protein and protein-RNA interactions within the CHIKV RC, in order to better understand the viral replication process and to facilitate structure-aided drug discovery against CHIKV and related infectious viruses. We will prepare the essential viral components, assemble and characterize the structure and function of the recombinant viral RC with the complementary biochemical, biophysical and structural methods to provide a high-resolution dynamic view of the virus replication complex. We will also use reverse genetic methods to validate the molecular model of CHIKV RC.

By achieving these aims, we will report the ultra-structure of a positive sense RNA virus replication complex and reveal the molecular basis for viral RNA transcription and replication. This work will provide an intellectual basis for future structure-based drug discovery against essential components and features of the CHIKV RC and vaccine design. The project focuses on CHIKV to enhance our understanding of the molecular mechanisms of viral transcription and replication. The findings will have broad implications in RNA virology in general.

Contact Us

If you have questions regarding this project, please email the Principal Investigator.

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