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Abstract

From Structure to Mechanisms of Zika Virus-Induced Neurodevelopmental Disease †

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Abstract: Zika virus (ZIKV) has explosively emerged over recent years, causing a series of epidemics across the Western world. Neonatal microcephaly associated with ZIKV infection has already caused a public health emergency of international concern. As with other members in the *Flaviviridae* family, ZIKV relies on its nonstructural protein 5 (NS5) for RNA genome capping (by the methyltransferase N-terminal domain) and replication (by the RNA-dependent RNA polymerase (RdRP) domain), representing an attractive crystallisable and antiviral target. The crystal structures of the ZIKV NS5 protein in two different space groups revealed conserved protein self-interactions to form dimers and higher-order fibrillar oligomers that serve as a platform for the coordination of the different enzymatic activities across neighboring molecules. The presence of dimers in solution was further verified by small angle X-ray scattering (SAXS), analytical ultracentrifugation (AU), and mass spectrometry, and ZIKV/NS5 helicoidal fibers were also observed by negative staining transmission electron microscopy (TEM) and atomic force microscopy (AFM). In addition, our preliminary data indicate that NS5 oligomerization might act as scaffold to interact with host proteins. In order to extend our findings, we have studied the in vivo effects of ZIKV NS5, both wild type and mutants in which NS5 oligomerization was disrupted, and these revealed an unexpected role of this protein in the exhaustion of neural progenitor cell (NPC) pool that may contribute to ZIKV-induced microcephaly. We have also identified a cluster of cilia/centrosome and nuclear envelope proteins of host cells as NS5 interactors. Work is currently ongoing to determine how NS5 interferes with the molecular machinery and behavior of NPCs to provide a better understanding of ZIKV–host interactions, highlighting new potential targets for therapeutic intervention.

Keywords: CNS growth; Zika virus; microcephaly