Keynote Lecture

KN-07

Virulence factors and host defenses to viral infection

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Viruses employ a variety of molecular strategies to carve out an existence in their host and to thwart host defenses. Crystal structures of viral proteins and of the host proteins deployed as molecular weapons contribute enormously to our understanding of viral pathogenesis and our efforts to combat viral infection. Mosquito-borne flaviviruses, including the dengue, Zika, yellow fever, Japanese encephalitis and West Nile viruses, cause serious human diseases in much of the world. A growing number of diverse functions has been discovered for the enigmatic virulence factor known as NS1: it is an essential cofactor in viral genome replication, a mediator of the host immune response, and a trigger of host vascular leakage. NS1 lacks precedent in the structure and sequence databases, so an accurate 3D structure was key to understanding the basis for its various functions. A high-throughput survey of expression conditions in baculovirus-infected insect cells was essential to identifying conditions for production of recombinant NS1 in its natural glycosylated, disulfide-linked form. The crystal structure of West Nile virus NS1 was solved from the anomalous scattering of the native sulfur atoms using an 18-crystal data set [1,2]. The structure revealed a new protein fold with a fundamentally dimeric architecture, and led us to assign functions to two of the three NS1 structural domains. Subsequent structures of NS1 from dengue virus and Zika virus established the basis for its membrane association in cells and its lipid encapsidation when secreted [3]. New functions for this remarkable virulence factor have emerged in follow-up studies that build upon the crystal structures.

[1] Akey, D. L. et al. (2014) Science 343, 881-885.
[2] Akey, D. L. et al. (2014) Acta Crystallogr. D70, 2719-2729.
[3] Brown, W. C. et al. (2016) Nature Struct. Molec. Biol. 23, 856-867.

Keywords: flavivirus NS1, sulfur SAD phasing