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Structural Studies on Virus Infections

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Editorial

Viruses are complex machines that effectively infect cells and hijack the cellular machinery to propagate themselves. Diverse pathogenic viruses cause an immense burden on public and livestock health. Delineating the infection mechanisms of these viruses paves the way for successful prevention and treatment strategies against these pathogens.

Structural information on viruses and their component proteins provide insights into the virus function and also provide potential targets to develop rational drug design. Using high resolution structural techniques, it is possible to study these viruses and their component proteins to understand their mechanism of action. For the past 50 years or so, x-ray crystallography has been the major tool to determine protein structures at high resolution. However, in the last decade or so, advances in cryo-electron microscopy and tomography have made it possible to visualize viruses along with their component proteins in near-physiological states and also to arrest viruses at different stages of their infectious life cycles to study them at an ultra-structural level.

My research training during my PhD started with structure determination of the rubella virus capsid protein using x-ray crystallography. The near atomic structure of the rubella virus capsid protein established the unique fold of the protein and shed light on how the protein could perform its varied functions. Subsequently, my work extended to studying rubella virus using cryo-electron tomography due to the pleomorphic nature of rubella virions. Rubella virus is an important human pathogen that can cause devastating effects on a fetus when contracted during pregnancy. However, due to the varying shapes and sizes of rubella virions, structural studies on the complete rubella virus were difficult as the common methods of structure determination; x-ray, crystallography and single particle cryo-electron microscopy, both depend on homogeneity of the sample for averaging. Thus, cryo-electron tomography was the best tool to study the virus.

In contrast, my work with flaviviruses such as Zika virus used single particle cryo-electron microscopy as flaviviruses are icosahedral viruses with high symmetry. 3D reconstruction of the immature Zika virus provided a model for the virus and highlighted differences in the capsid structure and external glycoprotein shell between the immature and mature forms of the virus and among other flaviviruses. This, in turn, helped to further understanding of another pathogenic teratogen.

With expertise that spans three major techniques of high resolution structure determination, I became interested to probe virus structures and processes that are more dynamic. Cryo-electron microscopic techniques are well-suited for these experiments as one can capture different aspects of a virus life cycle by freezing the sample under near native conditions. My current works with HIV-1 and influenza viruses are geared towards this direction.

HIV-1 is infamous for causing the globally debilitating AIDS. Though, clinical management of AIDS patients has advanced over the years, there is still no vaccine against the virus. Vaccine development against HIV-1 has suffered many challenges, one of the most important of which is the high mutability of the virus genome and its proteins. The envelope protein on the surface of the virus is involved with receptor recognition and attachment, but its structures are dynamic and variations among the different strains of HIV-1 have not been fully realized till now. Cryo-electron microscopic structure determination of different envelope protein sub-types will be helpful to compare and contrast between the different envelope structures for designing antigens that are broadly neutralizing and can be used as a successful vaccine.

Virus fusion is a dynamic process that involves changes in the virion and membrane compartment to fuse together. Though fusion is an important step in the virus life cycle that delivers the genome into the host cell, not much is known about the kinetic and mechanistic steps in the process. With cryo-electron tomography and sub-tomogram averaging, influenza virus fusion steps can be studied by freezing virus-membrane mixtures under different conditions to follow the fusion process. Such studies also help to identify critical junctures in the virus infection processes that could serve as potential targets for therapeutics. This experimental setup can also be applied to different systems to study other dynamic membrane-protein interactions. As cryo- electron tomography does not require any homogeneity of sample; asymmetric structures can be visualized and analyzed using this technique.

Insights into the molecular steps of a virus life cycle are important to appreciate the complexity of processes involved in successful infection of a host cell. My work on infectious viruses that affect primarily humans is, aimed in the long term, to study the early steps in virus infection which are primary areas for prevention and treatment. Ultra-structural details about virus entry and fusion can provide critical insights into the molecular life cycle of pathogenic viruses that can be potentially targeted for therapeutics.