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Editorial overview: Virus structure and function

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This special issue in *Current Opinion of Virology* is a collection of state-of-the-art reviews in understanding virus assembly and infection processes in light of an increasing number of structural investigations of viruses and their components by X-ray crystallography, NMR, Cryo-electron microscopy, electron and X-ray tomography and correlative imaging tools. These structures have the added advantage of potentially useful in aiding development of drugs or vaccines against infectious viruses.

Throughout the virus life cycle, increasing experimental evidence highlights the ability of viruses to expropriate cellular proteins to ensure their propagation. An intriguing first step of virus infection is its recognition of the host cells receptors. Because this first step in infection exposes viral susceptibility, host cell entry mechanisms have been on the agenda of structural biologists since the early eighties. In this issue, Mateo and co-workers review the Measles virus entry process and describe the cell adhesion process in a musical theme to explain how the viral membrane proteins target the host cell. A similar path of the viral life cycle is described by Theodore S. Jardetzky and Robert A. Lamb on Paramyxoviruses. They address the questions of receptor duality and the synergism between attachment and fusion proteins that drive virus-cell membrane fusion and virus entry. An interesting feature of the fusion process between virus and the host is the structural signature of the fusion proteins. Yorgo Modis gives an overview of multiple crystal structures of fusion type II proteins from different viruses including flaviviruses, alphaviruses and phlebovirus. These structures reveal that the fusion protein fold can be similar between two different virus families, but can also be quite different within the same virus family. These structural observations support the notion that viral fusion proteins could have evolved from multiple modules available in the host membrane that involved fusion processes.

Upon entry, negative strand RNA viruses (NSV) deliver their genomes, which are condensed by the nucleoproteins into nucleocapsids (non-segmented NSV) or ribonucleoprotein particles (RNP, segmented NSV). Progress in understanding the mechanisms by which segmented NSV nucleoproteins associate are addressed by Reguera and co-workers. They describe the now evident diversity observed in protein motifs and

their flexibility, which permits almost unlimited geometries of RNPs. The observed flexibility of nucleocapsids and RNPs is further linked to replication and discussed for bunyaviruses.

Another aspect of the requirement of flexibility for viral processes is described by Communie and co-workers. One important limitation to conventional high-resolution structural studies is the presence of disordered regions in protein targets. Intrinsic disorder is shown to be abundantly present in viral proteins and they describe the advantage of such intrinsic disorder for genome packaging and replication in Measles virus.

Frazer Rixon and Michael Schmid compare the cryo-EM structures of double-stranded DNA tailed bacteriophages and human herpes simplex virus to show a high structural similarity of the major capsid protein, which has a characteristic HK97 capsid protein fold, and of a 12-fold symmetric portal protein complex at a special vertex for genome packaging. This provokes two alternative hypotheses: that the lineages of the bacteriophages and herpes simplex virus split early from a common ancestor, or that herpesvirus evolved from bacteriophage at a time in the evolution time scale after the rise of eukaryotes, and was the only successful dsDNA, HK97 fold, portal-containing colonizer of the new ecological niche provided by eukaryotes.

Zeev-Ben-Mordehai and co-workers describe a hybrid approach using fluorescent light, electron and X-ray microscopy to examine the herpes simplex virus in the cell. Though neither method yields structural resolution as high as that for cryo-EM or X-ray diffraction methods, they provide spatial and temporal information regarding the virus replication process in the cell.

Hong Zhou reviews the latest advances in using single particle cryo-EM to resolve near atomic structures of membrane viruses like Dengue virus and Venezuelan equine encephalitis virus, which have revealed structural features unobtainable by X-ray structures of individual structural components or their domains. This points to the realization of the ultimate power of cryo-EM for virus structure research with unprecedented details. Furthermore, this review also describes the recent success and controversy in the cryo-EM studies of HIV Env trimer.

Vaccines and/or drugs, when they exist, are the current weapons against viruses. The massive use of antiviral molecules induces, most of the time, mutations in the viral components and so a resistance phenomenon. In the quest for new therapeutics, the proteins of the viral capsid have emerged as highly promising targets that could provide a new generation of antiviral agents across viral diseases. Klaus Klumpp and Thibaut Crepin explain how structural information has greatly facilitated the discovery of drugs targeting the HIV capsid protein. Moreover, this review exemplifies how the inherent flexibility of viral proteins can be used against viruses.

Biographies

Wah Chiu is the distinguished service professor at Baylor College of Medicine. He directs a research Center devoted to the methodology development for cryo-electron microscopy and tomography for viruses, molecular machines, organelles and cells. His Center is opened to

collaboration with investigators around the globe with appropriate specimens and engages in various training and dissemination activities. His virus structure research has been supported by the National Institutes of Health and the Robert Welch Foundation.

Thibaut Crépin has been recruited by CNRS in 2007. His research focuses on the molecular mechanisms associated to protein-RNA complexes. After working in the field of aminoacyl-tRNA synthetases and the translation, he has shifted to the replication of negative strand RNA viruses.

Rob WH Ruigrok is professor at the University of Grenoble since 2003. He is a structural biologist, working on protein-RNA complexes of negative strand RNA viruses with a special focus on Influenza, Rabies and Measles viruses.