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Editorial overview: Virus structure and expression

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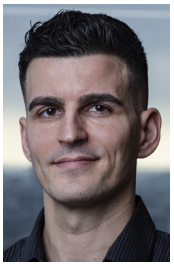

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Nicholas MI Taylor is an Associate Professor and Group Leader at the NNF Center of Protein Research at the University of Copenhagen (Denmark). He received his PhD in Molecular Biology at EMBL and the University of Heidelberg, where he was studying the RNA polymerase III transcription system. He then moved for a postdoc to CIB-CSIC (Spain), investigating RNA polymerase I structure. His next postdoc was at EPFL (Switzerland), where he used cryo-electron microscopy (cryo-EM) to reveal the structural transformation of the bacteriophage T4 baseplate upon host cell attachment. After this he went to the Biozentrum at the University of Basel (Switzerland), where he investigated the transport cycle of the human multidrug transporter ABCG2 using cryo-EM. His current research focus is the structure, function and modification of biological molecular machines involved in molecular transport across membranes.

Viruses are the most common biological entities on the planet. Their impact on global ecology and human life cannot be overestimated – as the current Covid-19 pandemic shows only all too clearly. Viruses have evolved to become highly efficient nanoscale instruments for the delivery of viral genetic material. Knowledge of the structure of the virus particle and detailed characterization of the principles that govern its assembly is crucial for understanding the function. This information is key to finding novel antivirals and other types of treatment for diseases caused by viruses. Several researchers have contributed their review articles to this issue and provided insight into virus structure, assembly, and function from different angles, ranging from capsid-targeting antivirals and neutralizing antibody interactions with virus capsid to the inherent asymmetry of otherwise highly symmetrical viral capsids and to the structure and function of host cell-binding organelles of bacterial viruses. We give short summaries of these contributions in the following paragraphs.

The use of small molecule compounds that interfere with the assembly, disassembly, and structural stability of the virus particle is an emerging strategy for the development of new antivirals. One of the main advantages of this approach is the high specificity of such compounds as their targets are unique to the virus. The challenge is the absence of an obvious starting point, unlike the case of substrate-derived antivirals inhibiting an enzymatic function in the virus lifecycle. On the other hand, the latter approach is limited in its scope as viruses exploit cellular functions extensively and use few own-encoded enzymes. Schlicksup and Zlotnick discuss various thermodynamic and structural aspects of binding of small molecule compounds to enteroviruses, hepatitis B virus, and HIV virus particles. These compounds are not known to inhibit enzymes, but their effect on virus assembly, maturation, or host cell recognition are profound. This approach has already resulted in effective antiviral therapeutics and many more are currently in the development pipeline.

Icosahedral symmetry is a common theme in the organization of many viruses. In all known spherical viruses, at least one protein shell comprising the virus particle has icosahedral symmetry. In these shells, protein subunits are organized according to the principle of quasi-equivalence. The shell consists of pentamers and, optionally, hexamers in which the subunits interact similarly but slightly different (hence, the quasi-equivalence). An icosahedrally symmetric virus shell contains a pentamer in each of its twelve vertices and a variable, but fixed for each virus, number of hexamers between the pentamers that is determined by the rules of the quasi-equivalence principle. One of the main consequences of high symmetry is that weak interactions between subunits have a synergetic effect making

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the virus particle sufficiently stable to survive transfer between hosts. On the other hand, the virus must be able to open its shell upon binding to a susceptible host cell. Interaction of the virus with its host receptor is asymmetric, and deviation from perfect icosahedral symmetry must be an inherent property of the virus shell. Jana and May describe the current status of the wide field of experimental studies and computer simulations of asymmetry in virus capsids. The ultimate goal of this research is to contribute to the design of antiviral compounds by specifically exploring the symmetry-asymmetry relationship of virus capsids.

Flaviviruses are arthropod-borne RNA viruses that may cause encephalitis and hemorrhagic fever. Today, the most famous of flaviviruses is Zika virus. It can spread from a pregnant woman to her baby, which may result in microcephaly and other birth defects. In adults, Zika virus may cause Guillain–Barré syndrome. However, other flaviviruses such as dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, and tick-borne encephalitic virus have caused debilitating illnesses in humans for centuries. The adverse effects of yellow fever virus, Japanese encephalitis virus and tick-borne encephalitis virus on human population in historically heavy affected areas such as Southeast Asia, Africa and Central/South America have been mitigated by the development of successful vaccines. Flaviviruses display strong antigen cross-reactivity, which represents a double-edged sword. On the one hand, antibodies against one flavivirus may protect from another flavivirus, but on the other hand, previous exposure to a similar flavivirus can lead to potentially deadly antibody-dependent enhancement of infection (ADE). To this end, dengue virus with its four serotypes represents a particularly challenging target for vaccine development because of the pronounced ADE. One of the important goals of dengue virus research is to have a vaccine that protects against all four serotypes without causing ADE. For this, all aspects of antibody interaction with the virus particle must be understood. Sevvana and Kuhn discuss the structure of several flaviviruses in complex with various antibodies in exquisite detail and demonstrate these interactions with the help of fantastic illustrations.

Alphaviruses are positive-sense RNA arthropod-borne RNA viruses, similar to flaviviruses, but the structure of the alphavirus particle and many functional aspects are different to those of flaviviruses. Unlike flaviviruses, alphaviruses are enveloped viruses. As such, the mechanisms of alphavirus and flavivirus entry to the eukaryotic cell are different. Depending on the symptoms and disease outcome, alphaviruses can be divided into two groups: arthralgia-causing and neuroinvasive. Chikungunya virus and Ross River virus cause fever, rash, and polyarthritis and are endemic to certain areas. Venezuelan equine encephalitis virus and Eastern equine encephalitis virus frequently cause encephalitis and death in mammals. Interestingly, the genome organization, replication, assembly pathway, and virion structure are very similar in all alphaviruses. Some of the important directions of research in the field of alphaviruses are studies of the processes of entry and assembly of the virus particle because alphaviruses are being developed into gene delivery vehicles. Button et al. describe what is currently known about the interaction of the virus with its host cell receptor, about the structure of the virus polyprotein during virus particle assembly, about the assembly of the nucleocapsid core and the process of budding of newly assembled virus particles.

Of all viruses, bacterial viruses or bacteriophages are the most numerous and tailed bacteriophages are the largest order of known bacteriophages. The

tail, an extremely intricate apparatus evolved for genome delivery into the host cell, can either be short and non-contractile, long and non-contractile or long and contractile. In recent years, great progress has been made in the structural and functional description of the infection mechanism of tailed bacteriophages, arguably mainly due to the 'resolution revolution' in cryo-electron microscopy. Huang and Xiang review the progress that has been made specifically in the structural biology of gram-positive bacteriophages, with a particular focus on the infection process. These phages face different challenges compared to the viruses of gram-negative bacteria. The cell wall of gram-positive bacteria is usually much thicker, but in contrast to gram-negative bacteria only a single membrane needs to be traversed.

Linares *et al.* also explore tailed bacteriophage structural biology but focus on the structure of bacteriophages that have a long, non-contractile tail, also known as the *Siphoviridae* or siphoviruses. Some of the best-known examples of this family are bacteriophages λ and T5, the study of which has greatly impacted the field of molecular biology in general. The tail of siphoviruses is essentially a very long tube, acting as a conduit for genomic DNA and proteins that reside in the capsid before host attachment. Different tail proteins have evolved specific functions in the regulation of DNA ejection out of the capsid. Bacteriophages use receptor-binding proteins (long and slender tail fibers or shorter and stockier tailspikes that have an enzymatic activity) to specifically recognize target cells, thus making sure that the genome is delivered to a cell that allows for productive assembly of phage progeny. Decoration domains on the tail tube protein appear to contribute to host cell specificity. The sheer complexity of these tails, and the finely tuned control and release systems that govern DNA delivery into host cells, continue to amaze.

Honeybees have a big impact on the world's ecosystem by playing a major role in the pollination of flowering plants. Furthermore, they produce honey, a worldwide multibillion dollar industry. The worldwide population of honeybees is under threat by environmental stress as well as several pathogens. Procházková *et al.* present a review on the structure and assembly of the virus families *Iflaviridae* and *Dicistroviridae*, which together with their vector, the parasitic mite Varroa destructor, form a major threat to the global honeybee population. Both virus families have icosahedral capsids which release their genome upon triggering by acidic pH. However, where Iflaviridae expand upon triggering, those of *Dicistroviridae* stay compact. Both families also use divergent strategies for infection, dicistroviruses have inner capsid proteins, whereas iflaviruses rely on domains or proteins on the virion surface to get across membranes and deliver the viral genome into the cytoplasm. A better understanding of the structural biology of honeybee viruses might one day allow the development way to potential antiviral therapies.

As is clear from these summaries, a vast range of topics is reviewed in this issue. We believe this breadth of research is crucial in a thriving scientific community, which ultimately not only benefits sciene but also society as a whole. Finally, we hope you will enjoy reading these contributions as much as we have.