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How viruses use cells

Editorial overview

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Jacomine Krijnse Locker heads the vaccinia virus assembly group at the European Molecular Biology Laboratory. Her research interest is to understand viruses at the cell-biological level. She focuses on two aspects of vaccinia virus. First is to unravel the way the complex life cycle of this virus is organized within the infected cytoplasm. A second main focus is to dissect the complex structure and assembly of this large DNA virus, using high-resolution electron microscopy techniques.

Most people probably regard viruses as nasty creatures: they can cause disease and mortality among large populations of people or in unfortunate individuals. AIDS (acquired immunodeficiency syndrome), H5N1 and SARS (severe acute respiratory syndrome) are words that might immediately come to mind. When studying viruses in detail, however, they have many fascinating aspects. Viruses cannot multiply without infecting cells, simply because they lack vital functions that are required for replication. In many cases this tight and obligatory interaction with their host has led to viral intracellular lives that are highly sophisticated. In some cases it seems that a better or more efficient way of producing infectious virus particles could not be imagined. In order to multiply, viruses use virtually very aspect of their host cells, which prompted me previously to call them the 'Weltmeisters' of cell biology [1]. Not surprisingly, by studying viruses we can learn a lot about cells. The following reviews highlight some of the complexities of different virus families. They cover a broad range of aspects of virus–host interactions: from membranes and the cytoskeleton to SUMO-modification and host-restriction. The last review in this series by Grüenwald and Cyrklaff describes the emerging high-resolution technique of cryo-electron tomography that is particularly well-suited to study the structure of viruses.

HIV affects 40 million people worldwide, being responsible for an estimated 3 million deaths per year. Despite extensive research, a protective vaccine or anti-viral drugs able to cure the disease are still not available. In this issue two reviews by Sokolskaja and Luban and by Fackler and Kräusslich highlight aspects of the complexity of this virus. An elusive part of the HIV life-cycle is the steps that follow virus entry, preceding integration of its reverse-transcribed genome into the host nucleus. These steps sequentially involve the penetration of the viral nucleocapsid into the cytoplasm, the uncoating and reverse transcription of the genome, and its transport towards and into the nucleus (reviewed in [2]). In certain cell types one or several of these steps can be blocked or 'restricted'. Sokolskaja and Luban review the roles of cyclophilin A and TRIM5 in HIV-1 restriction, cellular proteins that are able to bind to the (incoming) capsid protein. Paradoxically, whereas cyclophilin A inhibits infection in non-primate cells, it promotes infection in human cells. The search for additional factors that could explain this paradox led to the discovery of TRIM5, a monkey-specific gene that confers resistance to infection when expressed in primate cells. Although both cyclophilin A and TRIM5 were shown to bind to the capsid protein, it is not known how this leads to restriction of infection, a topic that is subject to ongoing research in the field of HIV-1 research.

Fackler and Kräusslich review the potential roles of the cytoskeleton in the retroviral life cycle. They summarize how HIV interacts with both microtubules and actin at virtually every step of the cytoplasmic stage of its life cycle. Microtubules and cytoplasmic dynein have been implicated in the transport of the reverse-transcribed genome, the pre-integration complex, towards the nucleus [3]. Although cytoskeletal elements probably also play a role in the transport of assembly intermediates prior to virus budding, nothing much is known about this topic. In order for the viruses to enter or exit cells — which usually occurs at the cell surface in most cell types that are susceptible to HIV-infection — the virus has to overcome the cortical actin barrier. Accordingly, actin might play a role during both entry and budding of the virus. Both microtubules and actin also play a crucial role in the formation of cell–cell contacts, the so-called virological synapse, through which virus-spread between cells is thought to be mediated.

The lack of a cell-culture system that can produce high-titered virus has clearly hampered research on the RNA virus HCV (hepatitis C virus). Like HIV, this virus has important medical relevance affecting ~170 million people worldwide. In this issue Bartenschlager reviews how systematic research in the HCV field resulted in the discovery of a cell–virus system that is able to generate infectious progeny. Without doubt, this system can be expected to shed more light on the elusive life-cycle of this virus and will hopefully also contribute to the understanding on how to cure or prevent this disease. An intriguing aspect of this recently discovered cell–virus system is that replication and virus production is highest in a certain cell type, Huh7.5, a clone of the human liver cell-line Huh7. It will be both important and interesting to understand what is 'special' about these cells, why these cells, in particular, are so efficient in producing infectious HCV.

Herpes viruses are among the most complex viruses, encoding for approximately 70 proteins. Not surprisingly, these viruses require many cellular functions and acquire two sets of cellular membranes in order to assemble and exit cells. Being large DNA viruses they replicate their genome in the nucleus where these are inserted into nuclear-assembled capsids. For many years one of the major controversies in the herpesvirus field was how these nuclear assembled nucleocapsids leave the cell and how the extracellular virus acquires its envelope. Mettenleiter *et al*. review the model that is currently favored; capsids leave the nucleus by budding at the inner the nuclear membrane. By fusing with the outer nuclear membrane, a membrane-free capsid is then released in the cytoplasm. The capsids acquire a double membrane derived from the trans-Golgi network or endosomes mediated by a wrapping event. Fusion of the outer most membrane with the plasma membrane then releases infectious progeny into the extracellular milieu. This prevailing model on herpesvirus assembly is consistent with steadily increasing amounts of molecular detail being revealved about underlying herpesvirus morphogenesis.

Viral membrane proteins have been used extensively to study protein folding and glycosylation, allowing important insights into these cellular processes. A specific protein modification is the addition of an 11 kD peptide called 'SUMO' (small ubiquitin-like modifier) to proteins. SUMO addition might have a multitude of functions, in most cases the addition of SUMO results in nuclear localization of cellular proteins. Accordingly, most viral sumoylated proteins described to date are encoded by DNA viruses that replicate in the nucleus. The review by Boggio and Chiocca highlights some of the recent findings on SUMO and viruses, and discuss how this modification can be beneficial to virus infection. For most DNA viruses that encode SUMO-modified proteins, the addition of SUMO results in nuclear localization, where the viral SUMO-target exerts its function. The authors discuss an increasing number of examples in which viral transcriptional regulators are modified by SUMO, a modification that generally leads to the repression of transcriptional activity.

Until recently high-resolution structure-analyses of viruses was mostly limited to viruses that are symmetrical in shape. With the technique of electron tomography (ET) this limitation can largely now be overcome. ET relies on an electron microscope that can tilt the specimen holder up to about 60–70 degrees. Multiple images of the sample are made at different tilt angles in order to computationally generate a three dimensional model [4,5]. Because all EM techniques are limited by the thickness of the sample, which should not exceed 0.5–1 μm, viruses with sizes ranging from 20–350 nm are ideal subjects for ET. Recent applications of this approach have led to new insights into the structure of herpes simplex virus, HIV and vaccinia virus as reviewed in this issue by Grünewald and Cyrklaff. A major challenge for future virus research is to use ET to reveal how viruses interact with cells, for example to reveal the structure of viral assembly and disassembly intermediates at high resolution and in three dimensions. For many viruses, entry and exit occurs at the cell surface, in areas of the cell that are thin enough for ET. Such processes can, thus be studied by 'whole-cell ET', without a need for sectioning the cells. By combining ET with cryo-EM, which involves preserving samples by rapid freezing, and by generating time-lapse series of entry or egress, cryo-ET can provide images of these processes in a close to native state, and in a time-resolved manner. The future prospect is that cryo-ET can complement live cell imaging at the light microscopy level, by providing high-resolution images of dynamic processes.

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