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Early Virus–Host Cell Interactions

Viruses are particles with diverse shapes and sizes, ranging from a few dozen nanometers to micrometers. They are made up of repetitive blocks of proteins, and sometimes, lipids and glycans. Their genomes show various structures and arrangements, encoding from a few genes to several hundred. Viruses are strict intracellular parasites, found in all types of life forms, from prokaryotes to plants and animals. As such, they are all reliant on subverting host cellular factors and functions for their own replication, amplification, and subsequent spread. Viral particles are committed to transfer the virus genome from an infected cell to a non-infected cell. Thousands of viruses have thus far been sequenced and there is arguably many more to be discovered. Although only a small minority of viruses causes serious life-threatening diseases and death, viral infectious diseases have huge implications for the human public health, agricultural productivity, and economy. Climate change, human activity, and urbanization are many factors promoting the re-emergence and emergence of new pathogenic viruses, as exemplified by the recent outbreaks of Ebola and Zika zoonotic viruses. Ideally, preventing virus infections requires approaches targeting early virus–host cell interactions, before the release of viral material and genome into the cytosol.

To invade cells and start their replication, viruses have to penetrate the intracellular compartment. The process consists of an intricate series of highly dynamics, tightly coordinated events, including among others virus attachment to cells, intracellular trafficking, and delivery of the virus genetic information. The whole sequence is known collectively as “virus entry.” Over the last 50 years, scientific attention to the cell biology of virus entry has grown considerably. With an increasing number of reports on the structure of viral particles, tropism, cellular receptors, and penetration pathways, the field has witnessed many exciting new findings and breakthroughs. The review by Helenius [1] provides a good overview of the evolution of the field over this period and is an excellent introduction to this special issue dedicated to the molecular mechanisms of early virus–host cell interactions.

Infection starts when viruses contact the host cell surface. This invariably implies binding to one or more cellular receptors, which includes proteins, carbohydrates, and lipids. Among receptors, the interactions between viruses and lectin-based receptors have been highly characterized [2]. The human C-type lectin DC-SIGN was the first cellular receptor visualized live

interacting with a virus [3]. Lasswitz *et al.* [4] review here proteomics and glycomics strategies to identify yet elusive receptors for adenoviruses. The most recent findings on other virus–receptor interactions are extensively discussed in the review by Maginnis [5]. The human immunodeficiency virus and its co-receptor CCR5 are taken as an example by Brelot and Chakrabarti [6] to address (i) how viruses can subvert receptors to escape the host immune response and also (ii) how receptors drive the virus-induced pathogenesis. The research article by Shimon *et al.* [7], which reveals the structure of the receptor-binding domain of a non-pathogenic mammarenavirus, further illustrates the discussion. This work sheds light on how viral pathogenicity can be driven through an extent of weak rather than strong interactions with a specific cellular receptor.

Most viruses are sorted into the endocytic machinery following their attachment to the cell surface. Reviews by Herrmann *et al.* and Fedeli *et al.* highlight the most recent advances on how the non-enveloped adenovirus-associated viruses [8] and emerging zoonotic arenaviruses [9] find their way in the endosomal machinery to penetrate and infect cells. In the first review, the possibilities to engineer genetically modified adenovirus-associated virus to manipulate early virus–host cell interactions and virus tropism are brought up, which opens interesting perspectives to target specific organs and develop novel tools in gene therapy. In the second review, arenaviruses perfectly demonstrate the importance of using viruses as functional cargo to decipher endocytic processes. That arenaviruses reach late endosomal compartments without passing through early endosomes suggests the existence of not-yet identified endocytic routes.

To gain access into the intracellular compartment, enveloped viruses have to fuse their envelope with the cell membrane. Several classes of viral fusion proteins are known to mediate this process [10]. The study by Lai and colleagues [11] has led to the identification of two fusion peptides in the envelope spike glycoprotein of the severe acute respiratory syndrome coronavirus. The authors established that the two peptides act in a cooperative manner to fuse membranes. The new molecular insights into the fusion protein of influenza virus from the work by Zawada *et al.* [12] also help to better define the fusion process for this virus. Together, these studies improve our general understanding of virus-mediated membrane fusion mechanisms. The review of Abou-Hamdan *et al.* [13] further discusses

viral fusion mechanisms, with a special emphasis on the viral fusion glycoprotein G of vesiculoviruses. Some viruses must also get rid, completely or partially, of a protein coat surrounding and protecting their genome before viral replication can begin. Queminn and colleagues [14] develop on the uncoating process of large DNA viruses and explain the advantages of using electron-based microscopy to investigate such mechanisms.

Once viruses gain access to the cytosol, the replication and infection begin. The race continues between the virus and host cell defenses. The identity of the winner often defines whom from the virus or the host will take over the other. This is perfectly illustrated by the works from the groups of Alain and Faure on the autophagy-related events [15] and battle for ribosomes and translation [16] during the early steps of virus infection. Viral entry processes have a significant impact on these subsequent mechanisms.

With this special issue, I had the clear idea in mind to avoid a “copy and paste” of the numerous reviews recently published on the topic. I strongly encouraged the contributing authors to give frank opinions and develop free discussions on the latest knowledge, technical issues, and technological challenges as well as future perspectives in the field of virus entry. Ultimately, the goal was to provide readers with alternative, novel points of view to tackle virus entry questions from a different angle. With three original research articles and 11 reviews, one can consider that this special issue on virus entry is a success. It covers many aspects of virus entry, of course, but also goes beyond this scope. Some of the reviews describe the potential for works on early virus–host cell interactions to develop new therapeutic approaches in a broad range of domains, such as gene therapy and oncolytic treatments. Several others document high-end technologies and their usefulness in investigations into infectious entry like the review proposed by Laketa [17] on the last developments of specific microscopy techniques and computer-based image analysis.

I, however, do not want to give the feeling that this special issue provides a complete picture of the field. This would be arrogant and pretentious. Some discussions are missing, often not deliberately, sometimes simply by lack of experts in specific areas. Virus-induced receptor-mediated signalization, intracellular trafficking of viral material post-entry (e.g., transport of virus genome into cell nuclei), and the overall relevance of these processes in complex 3D-tissues and organs *in vivo* are as many important topics. I just hope that, through these collective efforts, this special issue will provide the virus entry field an informed perspective of future research directions and stimulated research in some of the understudied or nascent domains. Lastly, it has been a great time to work on this special issue with the editor assistants from the *Journal of Molecular Biology*, namely, Hélène Hodak, Jasmin Bakker, and

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