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Virus entry — an unwilling collaboration by the cell

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How simple, lifeless particles such as viruses cause devastating diseases and epidemics that affect the everyday lives of most people remain incompletely understood despite intense research efforts. We have determined the genomic sequences of hundreds of viruses, analyzed their structures and composition, and probed their replication mechanisms. Yet, aside for vaccination, we have few means by which we can inhibit their spread and cure diseases that they cause. The success of viruses can be attributed to coevolution with their hosts to which they are optimally adapted. Moreover, the apparent simplicity of viruses is deceptive as they extensively exploit cellular processes. Indeed, the dependence on cell functions provides a form of camouflage because it is difficult to inhibit viruses without hurting the cells and thereby damaging the hosts. Clearly, the ideal time to halt a virus infection is at the entry stage.

The life cycle of horizontally transmitted viruses begins with the attachment and entry of infectious virus particles into susceptible cells. Viruses have solved the entry problem in a myriad of ways. Some are encased in a lipoprotein membrane that fuses with cellular membranes to deliver the internal contents including genomic material and associated proteins into the cytosol. Others, lacking an outer membrane, penetrate cellular membranes by lysis or by forming pores. It follows that a full understanding of the entry process requires knowledge of the structure of the virus particle as well as the cellular components to which it binds, the steps following the initial interaction, the penetration mechanisms and the release or uncoating of the genetic material.

From an era dominated almost entirely by electron microscopy, the field of virus entry has developed into a dynamic, highly interdisciplinary enterprise. As illustrated by the collection of chapters in this volume, the effort now comprises structural biology, biophysics, biochemistry, molecular and cell biology, physiology, systems biology, immunology, and medicine.

Although some viruses enter through the plasma membrane of host cells, many interact with cellular receptors thereby activating signaling pathways that trigger endocytosis of the virus followed by transport into a complex network of functionally interconnected endosomal organelles. At some point, the virus activates its membrane penetration machinery. While a few viruses only deliver their genetic material into the cytosol, most of them enter the cytosol either in intact form or devoid of their lipid envelope. The penetration step involves

conformational changes in structurally metastable viral capsids or surface proteins that are triggered by low pH, interactions with receptors, proteolytic cleavages, or other cues. The journey may continue to the nucleus or to specific locations within the cytoplasm. Entry is generally a stepwise process in which the dismantling of the virus particle occurs in parallel with the movement of the incoming virus deeper into the cell.

The reviews in this issue focus on a variety of viruses and virus families and describe individual steps in their entry program. Although viruses of the same family tend to use the same general pathways, the detailed mechanisms of binding, signaling, penetration, and uncoating differ.

Fusion between the viral envelope and a cellular membrane constitutes a key step in the entry of enveloped viruses. The viral glycoproteins responsible for mediating fusion have been extensively studied in several virus families. For many of them, X-ray crystal structures in different conformations are available. Theodore C. Pierson and Margaret Kielian discuss the entry pathways taken by flaviviruses, small single-stranded RNA viruses that are responsible for diseases such as encephalitis and Dengue fever. The authors describe in detail the fusion step, which is accompanied by a dramatic rearrangement of the surface glycoprotein of these acid-activated viruses.

The herpesviruses comprise a large, successful family of DNA viruses, some of which cause life-long infections of humans. Herpesviruses differ from some simpler viruses in that the receptor binding and fusogenic functions are distributed among several proteins. Samuel D. Stampfer and Ekaterina E. Heldwein describe how structural studies have illuminated the fusion process. In particular they focus on the gH/gL complex, which they propose acts as an adaptor that transmits the triggering signal from virus-specific proteins to the highly conserved gB fusion protein.

Two of the reviews describe entry of non-enveloped viruses. Max Nibert and Yuko Takagi discuss differences in entry of several closely related double-stranded RNA viruses. Surprisingly, these viruses employ a variety of entry mechanisms despite similarities in capsid structures. Maarit Suomalainen's and Urs Greber's contribution concerns membrane penetration mechanisms evolved by three non-enveloped virus families that employ different strategies: one has a positive single-stranded RNA genome (picornavirus) and two have double-stranded DNA genomes (polyomavirus and adenovirus).

Advances in technology have greatly contributed to progress in understanding virus entry. Eileen Sun *et al.* discuss the adaptation of high-end, live cell imaging methods to study virus entry. As viruses are too small to be resolved by light microscopy, the use of fluorescence microscopy in different modalities has opened the way to elegant studies in which the progress of single virus particles during entry can be tracked. Live cell imaging has expanded the toolbox importantly, and is now the main technology used in many entry studies. The authors also discuss potential problems and limitations of the technology.

Pathways of cell-to-cell transmission that do not involve free virus particles are reviewed by Peng Zhong *et al.* Results from their group and others have demonstrated that viruses have different ways by which they can make use of the host cell for transmission. Such

transmission can rely on inter-cellular adhesion, cell-to-cell fusion, cellular polarity and intra-cellular trafficking without release of viruses as freely diffusible particles. These mechanisms are clearly important during the transmission of viruses in tissues and organisms.

In many of the chapters, the possibility of using entry inhibitors as antivirals is raised and current efforts in this direction are discussed. The review by Timothy J. Henrich and Daniel R. Kuritzkes focuses on this issue explicitly, describing antivirals that target entry of HIV-1. Whereas some drugs interact with the virus itself, others target cellular proteins. There is optimism that drug-resistant mutants will be less likely to arise when the latter class of antivirals is used.

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Biographies

Ari Helenius has been full professor of biochemistry at the ETH Zurich since 1 November 1997. He is currently the head of several interdisciplinary projects in the field of protein folding and virus–cell interaction.

Bernard Moss is a NIH Distinguished Investigator and Chief, Laboratory of Viral Diseases. His research encompasses all aspects of the replication cycle of poxviruses and their use for vaccine development. He has made important contributions to the entry process of poxviruses, identifying more than 10 highly conserved proteins that form the entry-fusion complex.