Molecular Mechanisms of Virus Cell Entry studied at Single Virus Level

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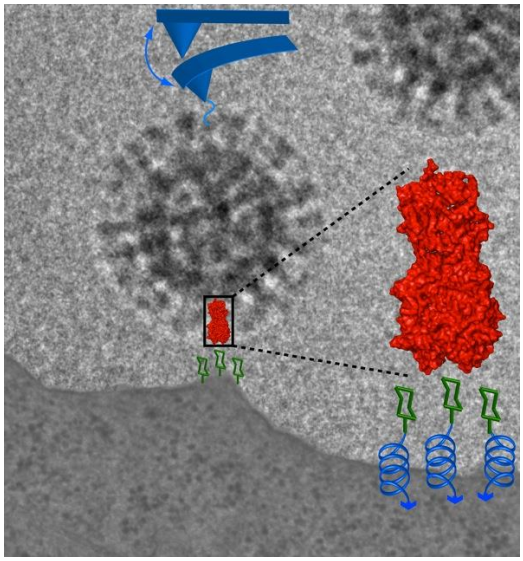
Modern techniques of fluorescence microscopy enable to study the entry and assembly of viruses in living cells at single cell and virus level. Single Virus Force spectroscopy provide quantitative data on virus-host cell interaction as well as on mechanical and structural alteration of the virus envelope along the entry pathway. These approaches will be presented exemplarily for influenza virus. Influenza virus belongs to a wide range of enveloped viruses. Virus-host cell binding marks the first critical step of infection. The major spike protein hemagglutinin binds sialic acid residues of glycoproteins of the host cell surface. We characterized the attachment of influenza virus to host cell by optical tweezers and atomic force microscopy-based single molecule force spectroscopy (see figure) revealing very low interaction forces. The observation of sequential unbinding events strongly suggests a multivalent binding mode between virus and cell membrane. However, an assignment of forces to their underlying molecular interactions involved in these processes is difficult or even cannot be obtained by these techniques. Force probe molecular dynamics simulations reveal a variety of unbinding pathways that indicate a highly dynamic interaction between HA and its receptor allowing to rationalize the binding of influenza virus to host cells quantitatively at molecular level. Subsequent steps of influenza virus entry, intracellular trafficking of viruses and the release of the virus genome from the envelope into the cytoplasm can be visualized by quantitative fluorescence microscopy at single virus level.



Graphic by Dr. Christian Sieben