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Weizmann Institute scientists reveal the invasion strategy of the world's largest virus

A Weizmann Institute study provides important new insights into the process of viral infection. The study, reported in the on-line journal *PLoS Biology*, reveals certain mechanisms by which mimivirus – a virus so called because it was originally thought to *mimic* bacteria in various aspects of their behavior – invades amoeba cells.

Living cells become infected by viruses in two steps. First, the virus penetrates the cell. Next, in the second and crucial step, the cell starts producing new viruses, which spread around, infecting additional cells. At the beginning of this production process, the cell makes the outer wall of the virus, a container of sorts composed of proteins and known as the capsid. The cell then makes copies of viral DNA and inserts it into the capsid. The result is a new, functioning virus that is ready to leave the host cell and infect more cells.

Understanding how viruses infect cells and how new viruses are produced in the course of the infection allows scientists to interrupt the infection cycle, blocking viral diseases. One of the difficulties, however, is that the invasion strategies of different viruses vastly differ from one another.

The mimivirus, known, among other things, for its exceptional size – it is five to 10 times larger than any other known virus – poses an interesting challenge in this respect. This virus was discovered only in the late 20th century, as its extraordinary size made it impossible to identify it by regular means. In addition, it contains much more genetic material than regular viruses, a feature that forces the mimivirus to develop particularly efficient methods for introducing its viral DNA into the host cell and for inserting the genetic "parcel" into the protein container during the production of new viruses in the host cell. Prof. Abraham Minsky and graduate students Nathan Zauberman and Yael Mutsafi of the Weizmann Institute's Organic Chemistry Department, together with Drs. Eugenia Klein and Eyal Shimoni of Chemical Research Support, have now revealed the details of some of the methods used by this virus. In their new study, the scientists have obtained, for the first time, three-dimensional pictures of the openings through which the viral genetic material is injected into the infected cell, and of the process in which this genetic material is inserted into the protein capsid.

In all previously studied viruses, viral genetic material was shown to be injected into the cell (during the cell's infection) and to enter the newly formed protein container (during the production of new viruses inside the cell) through the same channel, created in the viral container. In contrast, Institute scientists have now found that the giant mimivirus uses a different channel – located in a different part of its capsid – for each of these two goals. The scientists also discovered that the DNA helix in both these processes does not form a long thread, as in other viruses, but rather is organized into a densely packed block. The researchers believe that these unique traits serve to specifically

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facilitate both the injection into the host cell and the insertion of the large quantity of genetic material in the mimivirus.

In the study, electron microscope images of the mimivirus invading an amoeba cell showed that just after invasion, the walls of the protein capsid – a polygon composed of 20 triangles – separate from one another and open up like flower petals to create a large, star-shaped gate nicknamed the "stargate." The viral membrane underneath the gate fuses with the amoeba cell membrane, creating a broad channel leading inside the amoeba. The pressure released with the sudden opening of the walls – which is 20 times greater than the pressure pushing out the cork of a champagne bottle – pushes the viral DNA into the channel, whose large dimensions allow the genetic material to pass quickly into the amoeba cell.

Additional images show how the viral genetic material is inserted into the newly formed protein container when new viruses are produced in the host cell. In this process, the viral genetic material is delivered to its destination through an opening in the new container's wall opposite the "stargate." The insertion must overcome the pressure inside the container and is probably driven by an "engine" located within the wall that harbors the opening.

The scientists believe that the study of the mimivirus's life cycle, from cellular infection to the production of new viruses, may yield valuable insights into the mechanisms of action of numerous other viruses, including those that cause human diseases.

Prof. Minsky's research is supported by the Helen & Milton A. Kimmelman Center for Biomolecular Structure & Assembly. Prof. Minsky is the incumbent of the Professor T. Reichstein Professorial Chair.