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Researchers discover how compounds prevent viruses from entering cells

Compounds called defensins--known to prevent viruses from entering cells--appear to do so by preventing the virus from merging to cells' outer membrane, according to a study by researchers at the National Institute of Child Health and Human Development and the National Heart Lung and Blood Institute, both of the National Institutes of Health, and the University of California at Los Angeles.

The study, appearing in the September 11 Nature Immunology, also received funding from NIH's National Center for Research Resources.

"This discovery provides a basic understanding of a first-line defense against such viruses as HIV and the influenza virus," said Duane Alexander, M.D., Director of the NICHD. "This finding may ultimately lead to new strategies for preventing viral illness, and to increased understanding of why some individuals are more resistant to certain kinds of viral infection than are other individuals."

The means by which many viruses infect a cell is a two-step process, said the study's senior author, Leonid V. Chernomordik, Ph.D., Head of NICHD's Section on Membrane Biology in the Laboratory of Cellular and Molecular Biophysics. First, the membrane of the virus' outer coating, or envelope, must attach, or bind to, the outer membrane of the cell. After this attachment has taken place, the viral envelope membrane combines with, or fuses to, the cell membrane. After the two membranes have fused, the virus inserts its genetic material into the cell.

Defensins are produced by cells that are among the first to come in contact with viruses, Dr. Chernomordik explained. Such cells include leukocytes, a type of immune cell, and epithelial cells, which line the surfaces of many organs and tissues.

In the current study, the researchers studied epithelial cells from the inner surface of the lungs. The researchers discovered that defensins block the influenza virus entry into cells by preventing the fusion of viral and cell membranes. Specifically, the researchers studied the antiviral effects of two different classes of defensins, theta-defensin and beta defensin.

Membranes--the outer covering of cells and of many kinds of viruses--are coated with a layer of molecules called glycoproteins. The glycoproteins protrude from the membranes' surface, in somewhat the same way bristles stick out of a hairbrush. (See figure 1 at http://www.nichd.nih.gov/new/releases/defensins.cfm.) When the virus first infects the cell, glycoproteins on both the cell surface and on the virus spread apart, as the viral membrane approaches the cell membrane. To extend the hairbrush comparison, it's as if you could slide the bristles to the side, and leave bare patches on each hairbrush. At the bare patches, both the cell membrane and the viral envelope come together, and membrane fusion takes place.

Defensins, the researchers discovered, bind crosswise to glycoproteins, preventing the viral and cell glycoproteins from spreading apart. In keeping with the hairbrush comparison, it's as if the bristles of the hairbrushes were bound together with numerous small rubber bands. (See figure 2 at http://www.nichd.nih.gov/new/releases/defensins.cfm.)

"Defensins do not kill the virus, they just prevent it from entering the cell," Dr. Chernomordik said. "Viruses that are not allowed to enter the cells can then be destroyed by the cells of the immune system."

Dr. Chernomordik and his colleagues also studied the activity of mannan-binding lectin, a compound produced by the liver. Like defensins, mannan-binding lectin also protects against viral infection. The researchers discovered that mannan-binding lectin prevents viral infection in the same way that defensins do, by binding crosswise to glycoproteins.

Future studies of defensins may yield new strategies for preventing viral diseases, Dr. Chernomordik added. For example, by learning more about how defensins bind to glycoproteins, researchers one day may be able to devise new drugs that prevent viruses from entering cells.

Similarly, researchers might explore whether potential differences in defensin production might affect the ability to resist viral infection, Dr. Chernomordik theorized. For example, slight variations in the genes for defensins might make the molecules either more, or less, effective, at combating viruses. Similarly, some individuals may produce more defensins than do others.