Viral protein pair divulges Ebola secrets

While HIV and the Ebola virus may stand as equals in infamy, scientists know far more about the former than the latter. At least some of the mystery shrouding the dread Ebola virus may be lifting, however, as new evidence reveals how the virus evades detection and infects cells.

Apparently as crafty as it is deadly, the Ebola virus edits the information encoded in one of its mere seven genes to produce two distinct proteins. "It essentially makes two proteins for the price of one," says Gary J. Nabel of the Howard Hughes Medical Institute at the University of Michigan in Ann Arbor.

As part of an effort to develop an Ebola vaccine (SN: 1/10/98, p. 22), Nabel and his colleagues decided to examine this protein pair.

The researchers report in the Feb. 13 SCIENCE that one of the proteins suppresses the activity of neutrophils, a class of immune cells, while the other may serve as the hook that the Ebola virus uses to attach to and enter cells.

Though encoded by the same gene, the two proteins differ significantly. One is secreted from cells infected with the Ebola virus, and the other forms the surface of the new viruses manufactured by infected cells. Made in large amounts during the early phases of infection, the secreted protein is at least 300 amino acids smaller than the surface protein.

The importance of the secreted protein to the virus remains obscure, notes Hans D. Klenk of Philipps University in Marburg, Germany. Some strains of the Ebola virus produce large quantities of the protein, whereas other strains, equally deadly, do not, he explains.

Some investigators have proposed that the secreted protein resembles the surface protein closely enough that it could serve as a decoy, distracting the immune system from the virus. Seeking other roles for the protein, Nabel's group genetically engineered human cells to secrete large quantities of the molecule. The investigators then placed various kinds of immune cells in solutions containing the secreted Ebola protein.

Ignoring other immune cells, the secreted protein stuck to neutrophils, the white blood cells usually called into action at the start of infections. Nabel and his colleagues then identified a protein on the neutrophil surface that the viral protein latches onto. This binding prevents the neutrophils from being activated by various immune cell stimulants, they found.

The immune suppression wasn't absolute, however. If the cell stimulants were potent enough, they could rouse the quiescent neutrophils into action. Consequently, physicians trying to treat Ebola infections might consider ways of provoking neutrophil activity, says Nabel.

The larger Ebola protein does not appear to play a role in immune suppression. The researchers genetically engineered a mouse virus to flaunt this protein on its exterior. They then examined the ability of the hybrid virus to bind to and infect various cells.

While it infected many cell types, the hybrid virus most efficiently invaded endothelial cells, which line the inner surfaces of the heart, blood vessels, and other internal organs. A preference for blood vessel cells may help explain why massive hemorrhaging is a characteristic of Ebola infections.

"We think that's a very important clue," says Nabel, who suggests that investigators may one day use the viral surface protein to direct therapeutic compounds to infected cells.

The most important message of this new work is that the two Ebola proteins, though encoded by the same gene, have their own distinct cellular targets and therefore probably have different roles during infection and the course of the ensuing disease, says Klenk. —*J. Travis*

Peptide nanotube acts as tunnel for ions

Say the word "nanotube," and everyone assumes you're talking about a cylindrical molecule of carbon. However, some researchers have turned their attention to a different kind of nanotube—one made from stacks of ring-shaped protein fragments called peptides.

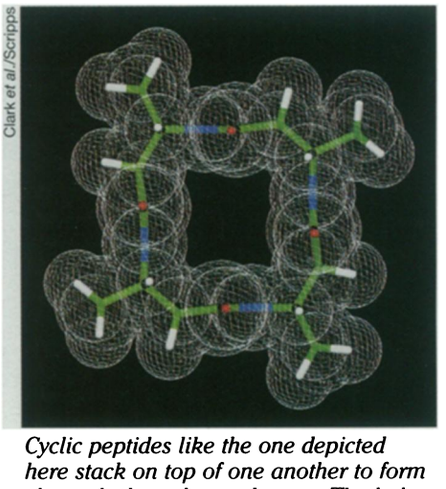
Investigators at the Scripps Research Institute in La Jolla, Calif., report that peptide nanotubes can act as channels, allowing small ions and molecules to pass from one side of a membrane to the other. This property, which is analogous to the function of numerous naturally occurring channel molecules in cell membranes, could make these nanotubes useful as sensors or even, by poking holes in cell walls, as antibiotics, says study coauthor M. Reza Ghadiri.

Ghadiri and his colleagues Thomas D. Clark and Lukas K. Buehler let ring-shaped peptides diffuse into a membrane made of a double layer of lipid molecules, where the peptides arrange themselves into tubes by forming hydrogen bonds with each other. Each ring, called a cyclic β^3-peptide, consists of four amino acids that differ from their natural counterparts by the addition of a carbon atom. Previously, the group had synthesized peptide nanotubes from a different class of amino acids joined in rings of eight.

The researchers determined the ion conductance of individual β^3-peptide nanotubes—"not a trivial measurement," says Samuel H. Gellman of the University of Wisconsin-Madison. They discovered that the new nanotubes conducted ions as effectively as the eight-ringed ones and more efficiently than gramicidin A, a natural peptide channel with antibiotic properties. The group's findings appear in the Feb. 4 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY.

The cyclic β^3-peptide nanotubes, first synthesized in solid form last year by Dieter Seebach and his colleagues at the Federal Institute of Technology (ETH) in Zurich, complement the eight-ringed ones and could have certain advantages over them, Ghadiri says. The β^3-peptide rings orient themselves in such a way as to give the tubes a slight positive charge at one end and a negative charge at the other—in other words, a dipole. "We're interested in what the dipole buys for you," Ghadiri says. It could influence which ions pass through the channels or the direction in which the ions travel.

The channels' unusual structure helps them resist enzymes that normally degrade proteins in a cell. This trait would be beneficial if the nanotubes were used as antibiotics, killing cells by damaging their walls, Ghadiri says. The group is exploring further the biophysical characteristics and biological activity of the nanotubes.



Cyclic peptides like the one depicted here stack on top of one another to form channels through membranes. The hole in the center, 0.26 nanometer in diameter, is large enough to allow small ions and molecules to pass through.

"It's an important step forward to show that these structures will conduct ions," says Gellman. Simply adding one atom to the amino acid building block of the peptides might be considered only "a baby step away from proteins," he says, but "it's not as simple as it may seem." Structures like these could mimic protein function and perhaps improve on it. —*C. Wu*