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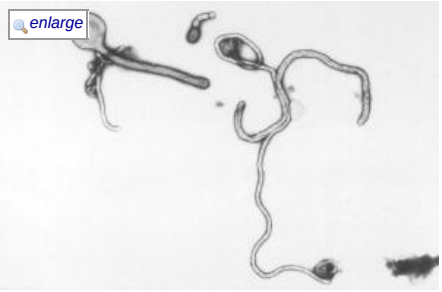
Scientists Identify Point of Entry for Deadly Ebola Virus

ScienceDaily (Aug. 24, 2011) — Ebola virus, the cause of Ebola hemorrhagic fever (EHF), is one of the deadliest known viruses affecting humans. Like anthrax and smallpox virus, Ebola virus is classified by the U.S. Centers for Disease Control and Prevention (CDC) as a category A bioterrorism agent. Currently, there is no vaccine to prevent EHF, and patients are treated only for their symptoms.Although outbreaks are rare, Ebola virus, the cause of Ebola hemorrhagic fever (EHF), is one of the deadliest known viruses affecting humans. According to the World Health Organization (WHO), approximately 1,850 EHF cases with more than 1,200 deaths have been documented since the virus was identified in 1976.



This negatively-stained transmission electron micrograph (TEM) revealed some of the ultrastructural curvilinear morphologic features displayed by the Ebola virus discovered from the Ivory Coast of Africa. (Credit: Charles Humphrey)

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EHF's clinical presentation can be devastating: fever, intense weakness, and joint and muscle aches progress to diarrhea, vomiting, and in some cases, internal and external bleeding caused by disintegrating blood vessels. Currently, there is no approved vaccine and patients are treated only for their symptoms. Like anthrax and smallpox virus, Ebola virus is classified as a category A bioterrorism agent by the U.S. Centers for Disease Control and Prevention (CDC).

Until now, however, researchers had only a limited understanding of how Ebola virus gains entry to a host cell.

Using an unusual human cell line, Whitehead Institute scientists and collaborators from Harvard Medical School, Albert Einstein College of Medicine and U.S. Army Medical Research Institute of Infectious Diseases, have identified the Niemann-Pick C1 (NPC1) protein as crucial for Ebola virus to enter cells and begin replicating. The discovery may offer a new and better approach for the development of antiviral therapeutics, as it would target a structure in the host cell rather than a viral component.

The findings are reported online in *Nature* this week.

Where all of us inherit one copy of each chromosome from each of our two parents, cell lines exist with only a single set, and thus with a single copy of each individual gene, instead of the usual two. Using an unusual human cell line of this type, Whitehead Institute researchers and their collaborators performed a genetic screen and identified a protein used by Ebola virus to gain entry into cells and begin replicating. The discovery may offer a new approach for the development of antiviral therapeutics.

"Right now, people make therapeutics to inactivate the pathogen itself. But the problem is that pathogens can quickly change and escape detection and elimination by the immune system," says former Whitehead Fellow Thijn Brummelkamp, now a group leader at the Netherlands Cancer Institute (NKI). "Here we get a good idea of the host genes that are needed for the pathogen to enter the cell for replication. Perhaps by generating therapeutics against those host factors, we would

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have a more stable target for antiviral drugs."

The method developed by the Brummelkamp lab to identify host factors relies on gene disruption -- knocking out gene function in the host cells, one gene at a time -- and documenting which cells survive due to mutations that afford protection from viral entry.

But human cells are diploid with two copies of each chromosome and its genes. Researchers can reliably target and knock out one copy of a gene, but doing so for both copies is far more difficult and time-consuming. If only a single copy is silenced, the other continues to function normally and masks any effect of the knockout.

To sidestep this obstacle, Jan Carette, a first co-author on the *Nature* paper and a former postdoctoral researcher in the Brummelkamp lab, employed a technique he had previously applied to study the cytolethal distending toxin (CDT) family that is secreted by multiple pathogenic bacteria, including Escherichia coli, Shigella dysenteriae, and Haemophilus ducreyi. Each bacterial species has developed its own twists on the CDT structure, which may link to the target tissues of the toxin's bacterium.

In his CDT work published in *Nature Biotechnology*, Carette together with co-lead authors of Whitehead Member Hidde Ploegh's lab, used a line of haploid cells isolated from a chronic myeloid leukemia (CML) patient. Because these cells, called KBM7 cells, have only one copy of each chromosome except chromosome 8, the researchers could disrupt the expression of each gene and screen for mutants with the desired properties, in this case survival of a lethal dose of toxin.

After knocking out individual genes by disrupting the normal structure of the gene, the resulting mutant KBM7 cells were exposed to various CDTs. In the cells that survived, Carette and coauthors knew that genes that had been disrupted were somehow crucial to CDT intoxication. By analyzing the surviving cell's genomes, Carette and coauthors identified ten human proteins that are used by CDTs during intoxication, and those host factors seem to be tailored to each CDT's targeted cell.

"I found it surprising that there is quite some specificity in the entry routes for each toxin," says Carette. "If you take CDTs that are very similar to each other in structure, you could still see significant differences in the host factors they require to do their job. So it seems that every pathogen evolved a specific and unique way of its toxin entering the cells."

To study Ebola virus, Carette and co-lead authors from Harvard Medical School and the Albert Einstein College of Medicine made use of an otherwise harmless virus cloaked in the Ebola virus glycoprotein coat. Using this virus and by altering the haploid cells somewhat, Carette and coauthors were able to pinpoint the cellular genes that Ebola virus relies on to enter the cell.

Carette and coauthors identified as necessary for Ebola virus entry several genes involved in organelles that transport and recycle proteins. One gene in particular stood out, NPC1, which codes for a cholesterol transport protein, and is necessary for the virus to enter the cell's cytoplasm for replication. Mutations in this gene cause a form of Niemann-Pick disease, an ultimately fatal neurological disorder diagnosed mainly in children.

Collaborators at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) tested the effects of active Ebola virus on mice that had one copy of the NPC1 gene knocked out. Control mice, with two functioning copies of the NPC1 gene, quickly succumbed to infection, while the NPC1 knockout mice were largely protected from the virus.

"This is pretty unexpected," says Carette, who is currently an Acting Assistant Professor in Microbiology & Immunology at Stanford School of Medicine. "This might imply that genetic mutations in the NPC1 gene in humans could make some people resistant to this very deadly virus. And now that we know that NPC1 is an Ebola virus host factor, it provides a strong platform from which to start developing new antivirals."

This research was supported by the National Institutes of Health (NIH), the U.S. Army, Boehringer Ingelheim Fonds and a Burroughs Wellcome Award.

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