

OCTOBER 18, 2007

## Researchers Discover a New Survival Strategy of Legionnaires' Disease Bacteria

In nature, invading pathogens often use the cells of their host to make themselves at home. Once ensconced in their new surroundings, however, bacteria require the aid of the host cell. For some forms of bacteria, host cells can unwittingly lend the invading bacteria the means to construct an intracellular hideaway where they can safely go about the business of making more pathogens.

Now, Howard Hughes Medical Institute (HHMI) researchers have discovered how a protein from the bacterial pathogen that causes Legionnaires' disease enables the pathogen to take over a cell's membrane protein traffic. The discovery by HHMI research associate Matthias P. Machner in the lab of HHMI investigator Ralph R. Isberg at Tufts University School of Medicine may help to devise new strategies to thwart the Legionnaires' pathogen and other bacteria.

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**— Ralph R. Isberg**

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Legionnaires' disease is a pneumonia-like illness caused by the bacterium *Legionella pneumophila*. The organism was first isolated in the late 1970s as the pathogen responsible for an outbreak of pneumonia at an American Legion convention in Philadelphia in 1976.

The new findings, which were published in *Science Express* on October 18, 2007, reveal a previously unknown capability of a pathogen to use a host cell for its own purposes. The work also reveals a mechanism that may be used by other bacteria and parasites, and may hold out the potential for broad new strategies to thwart infection.

Isberg explained that the pathogen uses one of its own proteins, known as SidM (or DrrA), in a novel way to take over protein trafficking pathways in a host cell.

*Legionella pneumophila* infects the human lung, where its favorite host cells, called macrophages, are abundant. Macrophages are immune system cells that usually mop up invading pathogens by absorbing and sequestering them in intracellular compartments known as vacuoles. The vacuoles then dock with other intracellular structures loaded with factors that kill bacteria. But the Legionnaires' bacterium has figured out a way to choke off those antibacterial factors so it can grow and multiply, snug in its membrane bound home inside a cell.

In nature, the Legionnaires' bacterium is widespread and typically lives in water-loving, single-celled amoeba. The bacterium can infect humans when bacteria-infected amoebae are inhaled in an aerosol that may occur, for example in a shower.

What the bug has probably done is mimic what's going on in amoeba. Amoebas have a lot in common with human cells, Isberg said. The pathogen is taking advantage of the proteins it has acquired over the millennia to take over membrane traffic in a host cell.

In infected cells, the bacterium uses its SidM protein to recruit a human protein known as Rab1 to the vacuoles where the pathogen hides. Inactive forms of Rab1 are maintained in the cytoplasm of the host cell, bound to other proteins that keep them in their inactive state. In an uninfected cell, scientists think specialized human proteins are required to jump-start Rab1.

Rab proteins just aren't floating around in the cell, said Isberg. They are bound to another protein.

Enter the bacterial SidM protein, which, according to Isberg's group's experiments, seems to mimic the human protein that activates Rab1 by decoupling it from the attendant protein that keeps it inactive.

These (Rabs) are small activating proteins in the cell that control how membrane vesicles get from one place to another, Isberg said. After these vesicles are packaged and released, they have to move to other sites within the cell.

In essence, according to Isberg, the pathogen is tricking the host cell: The pathogen grows in a membrane compartment that, in turn, steals (more) membrane from the endoplasmic reticulum, an extensive array of internal membranes found in eukaryotic cells.

The pathogen requires more membrane, Isberg explained, because it is multiplying and needs to make room: The compartment has to grow to accommodate more bacteria, he said.

The discovery that the bacterial protein SidM can effectively compete with human proteins in the complex and frenzied environment within a cell, Isberg said, is remarkable: In order to be successful, the pathogen has to compete with what's going on in a host cell. These (bacterial) proteins work in ways that are very similar to host cell proteins.

We don't think this is an unusual strategy, said Isberg, who authored the new *Science Express* report with Machner. It's probably not limited to bacteria.