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How *Legionella* manipulates cells

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The way that the intracellular pathogen *Legionella pneumophila* - the causative agent of Legionnaire's disease - co-opts the cellular machinery of human cells to avoid detection and destruction has been assumed to be basically the same in protozoans and mammals. But in the February 27 issue of Science, John Chen and colleagues from Columbia University report that the proteins involved in protozoan infection are different from those involved in mammalian infection (*Science* 2004, **303:**1358-1361).

The findings suggest that while mechanisms elucidated in protozoa can point the way for follow-up studies in mammalian cells, they cannot replace them, according to Margaret Clarke, from the Oklahoma Medical Research Foundation and a coauthor of the study.

"We got started because of a long-standing belief that *Legionella* redirects organelle traffic in host cells," said Howard A. Shuman, from Columbia University and senior author of the study. "Since we had the genome, we wondered if the bacteria had learned to use the SNARE system to do this?" he said, referring to the key components of intracellular organelle trafficking.

Chen and colleagues scanned the *Legionella* genome and identified two open reading frames with limited homology to SNARE components. The team then investigated the role of these open reading frames, *lep*A and *lep*B, during the replication of *L. pneumophila*.

The authors confirmed that LepA and LepB were delivered to host cells and then examined the growth of mutant *Legionella* strains lacking either or both genes in various hosts. They observed that intracellular replication in mammalian phagocytic cells occurred at normal levels. But when the protozoa *Acanthamoeba castellani* and *Dictyostelium discoideum* were infected, smaller numbers of bacteria were recovered, "suggesting a role for these proteins in a protozoan pathway," said Shuman.

When intracellular replication of *lep*A/*lep*B mutants in *D. discoideum* was examined with transmission electron microscopy, numerous vesicles containing bacteria remained after lysis of host cells. This was not observed with wildtype *L. pneumophila*and further pointed to LepA/B's involvement in an exocytic pathway in this protozoan.

"Amoebae require efficient means not only of phagocytozing and digesting bacteria, but also of excreting the indigestible waste," said Clarke. "We speculate that the Lep proteins allow the modified phagosome in which *L. pneumophila* replicates to engage this excretory pathway and be expelled from the cell."

The results show promise for the development of a simpler model system to study *L. pneumophila* interactions with host cells, said Craig R. Roy, an associate professor of microbial pathogenesis at Yale University who was not involved in the study. "And it will be very interesting to find out how these proteins are regulated at the level of expression and function, since you would expect tight control of these functions by the bacteria," he said.

"Lep proteins appear to be a pair of effectors that function primarily in amoebae, and this is the first clear demonstration of species specificity of effectors in *L. pneumophila*," said Ralph Isberg, from Tufts University.

Isberg, who was not involved in the study but who recently identified various effectors used by the Dot/Icm type IV secretion pathway fundamental to this system, said, "the main biological significance is that protozoa are the natural hosts of *Legionella* [and] virulent *Legionella* may have evolved from the other species by acquisition of effectors specific for mammalian cells."

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