

Legions of Hijackers

THE MULTI-LAYERED SUCCESS STRATEGY BEHIND THIS INGENUOUS PATHOGEN IS BEGINNING TO UNFOLD.

To set up house in a host cell, the bacteria responsible for Legionnaires' disease take an aggressive tack—they hijack the host's intracellular trafficking system and build themselves cozy hideouts.

Matthias P. Machner, a research associate in the lab of HHMI investigator Ralph R. Isberg at Tufts University School of Medicine, discovered how a bacterial protein commandeers host cell activities for its own purposes: to both hide and multiply.

Legionnaires' disease is a type of pneumonia caused by the bacteria *Legionella pneumophila*. The disease and the bacteria were named after an outbreak of pneumonia at an American Legion convention in Philadelphia in 1976, where the pathogen was first identified.

In healthy human cells, the regulatory protein Rab1 controls the movement of vesicles—cellular cargo containers composed of membrane—between different cell compartments. Other cellular proteins cuddle up to Rab1 to keep it inactive when no cargo needs to be “shipped.” Activating Rab1 requires one cellular protein to grab it and another to activate it. During infection, *Legionella*'s SidM (DrrA) catalyzes both steps in one fell swoop.

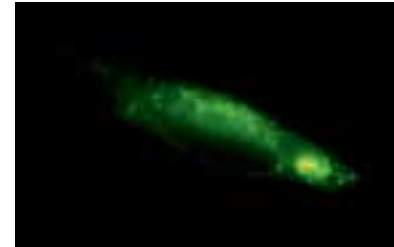
Finding a protein that can both grab and activate host protein is rare, says Isberg—and handy. Once *Legionella* establishes an infection within a membrane-bound vacuole of the host cell, the rapidly

multiplying pathogen needs to seize more membrane to avoid outgrowing its confines, much as an expanding family adds on to a house. By hijacking Rab1, *Legionella* not only acquires the means to add on but also gains control of a critical conductor of vesicle traffic. Thus, the organism can avoid destruction caused by the merger of its cellular home with a vesicle whose job is to degrade invading microbes.

While ingenious, SidM (DrrA) appears to be only one chapter in the story of how *Legionella* thrives—even if you knock out SidM, the bacteria continue to grow.

“This is like a Russian matryoshka doll story,” says Isberg of the pathogen's layers of defenses. “This organism has many backup systems for recruiting membrane. And 10 percent of its genome encodes proteins that manipulate the [host] cell.” ■

—LISA SEACHRIST CHIU



Inside a mouse macrophage, *Legionella pneumophila* (red) hides in a membrane sac surrounded by regulatory protein Rab1 (green).

IN BRIEF

HOW STRESS SUPERCHARGES LEARNING

Whether it's a burn from a hot stove or a snarling dog, an emotional encounter supercharges learning in a way that indelibly imprints those experiences in memory. Now researchers have pinpointed a molecular pathway in the brain that underlies stress-induced learning enhancement.

Led by Roberto Malinow of Cold Spring Harbor Laboratory and Richard Huganir, an HHMI investigator at Johns Hopkins University School of Medicine, the researchers published their findings October 5, 2007, in *Cell*.

The team first sought to establish a link between norepinephrine and phosphorylation of a subunit of one of the major neurotransmitter receptors in the brain, called the AMPA receptor. When the researchers treated rat hippocampal tissue with norepinephrine, the compound induced phosphorylation in the AMPA receptor subunit.

The researchers went on to show that fear responses in mice are associated with phosphorylation of the AMPA receptor subunit. Exposing the animals to fox urine, which provokes the fear response, triggered AMPA subunit phosphorylation, just as the epinephrine injections did. In addition,

they found that mutations that prevented receptor subunit phosphorylation also prevented epinephrine from triggering enhanced learning in the mice.

Researchers have long known that fear triggers release of norepinephrine along with epinephrine, producing the fight-or-flight response. “And it was known that norepinephrine affects the brain, activating learning to enable those stressful memories to be recalled more readily,” says Huganir. “Now we have shown how norepinephrine activates that learning—by producing a critical biochemical priming effect on AMPA receptors during states of stress.”

EVOLUTION TRANSFORMS “JUNK” DNA

Scientists have traced the 170-million-year evolution of a piece of “junk” DNA to its modern incarnation as an important regulator of energy balance in mammals.

HHMI international research scholar Marcelo Rubinstein and his colleagues reported their discoveries October 5, 2007, online in *PLoS Genetics*. Rubinstein is at the Institute for Research on Genetic Engineering and Molecular Biology of the National Council for Science and Technology in Argentina and the University of Buenos Aires.

All genomes are liberally sprinkled with DNA fragments derived from mobile elements that move randomly within the genome. Once considered useless, these “junk” sequences are now believed to provide raw material for the evolution of novel gene functions.

Rubinstein and his colleagues had been studying one such piece of DNA, called nPE2, which enhances the activity of a gene called *POMC* (proopiomelanocortin). Expressed in the brain, *POMC* produces peptides that regulate a variety of behaviors, including food intake and stress-induced analgesia.

The team found that nPE2 is highly conserved in mammals but absent in other vertebrates. When they compared nPE2 sequences from 16 mammalian species, they found the critically important nPE2 enhancer sequence to be the most rigorously conserved over evolutionary time. The findings, Rubinstein says, indicate that nPE2's function “contributed to the fitness of all mammals, probably by better tuning the central regulation of energy balance.”

SURVEYING THE GENETIC LANDSCAPE OF BREAST AND COLON CANCERS

An extensive study of the DNA in cancerous cells has uncovered a large