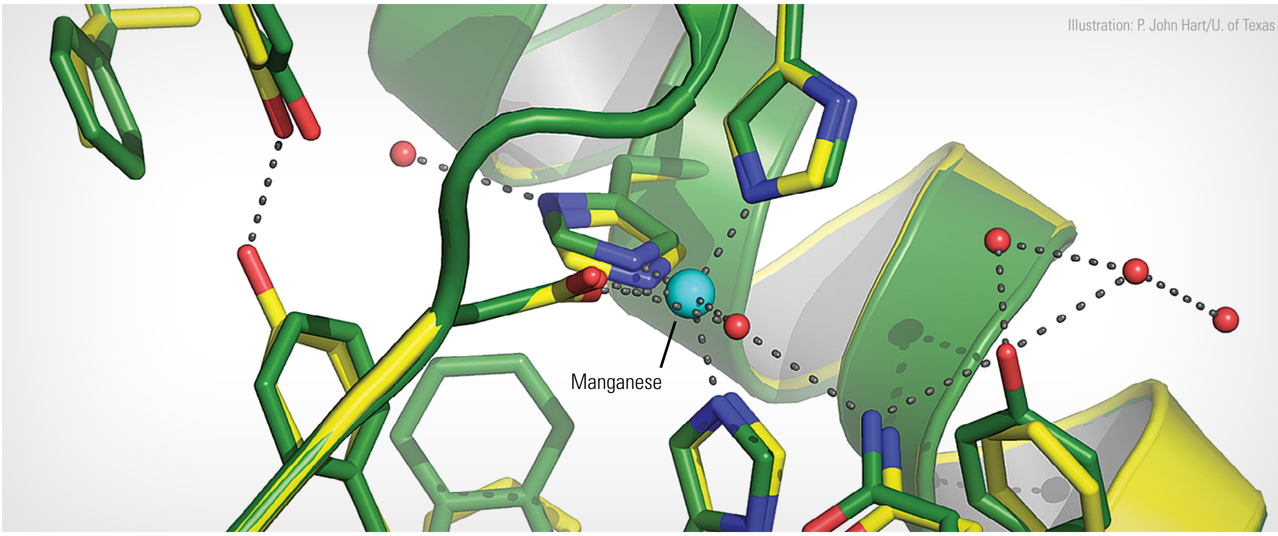
An Oddity about Lyme Disease Bacteria

UNLIKE ANY OTHER KNOWN LIFE FORM, THEY DON'T REQUIRE IRON

by Lonny Lippsett



Borrelia burgdorferi use manganese (blue dot), rather than iron, as linchpins bonded into the 3-D chemical architecture of critical enzymes.

Scientists have confirmed that the pathogen that causes Lyme disease can exist without iron, a metal that all other life needs. By substituting manganese for iron to make essential enzymes, the bacteria can elude immune system defenses.

To cause disease, *Borrelia burgdorferi* requires unusually high levels of manganese, scientists at Johns Hopkins University (JHU), Woods Hole Oceanographic Institution (WHOI), and the University of Texas reported. Their study, published March 2013 in *The Journal of Biological Chemistry*, may explain some mysteries about why Lyme disease is slow-growing and hard to detect and treat. The findings also open the door to search for new therapies to thwart the bacterium by targeting manganese.

"When we become infected with pathogens, from tuberculosis to yeast infections, the body has natural immunological responses," said Valeria Culotta, a molecular biologist at the JHU Bloomberg School of Public Health. The liver produces hepcidin, a hormone that inhibits iron from being absorbed in the gut and also prevents it from getting into the bloodstream. "We become anemic, which is one reason we feel terrible, but it effectively starves pathogens of iron they need to grow and survive," she said.

Borrelia, with no need for iron, has evolved to evade this defense mechanism. In 2000, groundbreaking research on *Borrelia*'s genome by James Posey and Frank Gherardini at the University of Georgia showed that the bacterium has no genes that code to make iron-containing proteins and typically does not accumulate any detectable iron.

Culotta's lab at JHU investigates what she called "metal-trafficking" in organisms—the biochemical mechanisms that cells and pathogens such as *Borrelia* use to acquire and manipulate metal ions for their biological purposes.

"If *Borrelia* doesn't use iron, what does it use?" Culotta asked.

To find out, Culotta joined forces with WHOI chemist Mak Saito. He was intrigued because of the high incidence of Lyme disease on Cape Cod, where WHOI is located, and because he had developed new techniques to explore metalloproteins in marine life. Metalloproteins contain iron, zinc, cobalt, or other metals that serve as linchpins for enzymes. They help determine the enzymes' distinctive three-dimensional shapes and the chemical reactions they catalyze.

It's difficult to identify metals within proteins because typical analyses break apart proteins, often separating metal from protein. Saito and WHOI research associate Matt McIlvin used a liquid chromatography mass spectrometer to distinguish and measure separate individual *Borrelia* proteins according to their chemical properties and infinitesimal differences in their masses. Then they used an inductively coupled plasma mass spectrometer to detect and measure metals down to parts per trillion. The combined analyses not only measured the amounts of metals and proteins, they showed that the metals are components of the proteins.

"The tools he has are fantastic," Culotta said. "Not too many people have this set of tools to detect metalloproteins."

The experiments revealed that instead of iron, *Borrelia* uses that element's next-door neighbor on the periodic table, manganese, in important *Borrelia* enzymes. One of these is superoxide dismutase. It protects the pathogens against another cellular defense mechanism: bombarding pathogens with superoxide radicals—highly reactive molecules that cause damage within the pathogens. Superoxide dismutase is like an antioxidant that neutralizes the superoxides so that the pathogens can continue to grow.

The discoveries open new possibilities for therapies, Culotta said. "The best targets are enzymes that the pathogens have, but people do not, so they would kill the pathogens but not harm people." *Borrelia*'s distinctive manganese-containing enzymes such as superoxide dismutase may have such attributes. ▲

This research was funded by the National Institutes of Health, the National Science Foundation, and the Gordon and Betty Moore Foundation.