SOUTHWESTERN NEWS

Media Contact: Amanda Siegfried
214-648-3404
amanda.siegfried@utsouthwestern.edu

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Researchers identify protein crucial for survival of Lyme-disease bacterium

DALLAS – April 25, 2005 – When the tick-borne bacterium that causes Lyme disease lacks a specific protein that responds to an incoming meal of blood, it is unable to be transmitted from the tick to a new animal host, researchers at UT Southwestern Medical Center have found.

The findings suggest that the protein, called BptA, is essential for the bacterium *Borrelia burgdorfei* (*Bb*) to survive in the gut of its tick host and may offer a potential new target for agents aimed at eradicating Lyme disease.

Results of the multisite study are currently online and will appear in an upcoming issue of the *Proceedings of the National Academy of Sciences.*

The bacterium that causes Lyme disease lives in infected mammals and in the midgut of ticks. When an infected tick bites an animal or a human, the bacteria are transmitted to the new host. Infection causes fever, malaise, fatigue, headache, muscle and joint aches, and a characteristic "bull's-eye" rash that surrounds the site of infection.

In the study, researchers genetically altered the *Bb* bacterium to make a "knockout" form that lacked a gene that codes for the protein BptA. Without the protein, bacteria were unable to utilize the blood on which the tick feeds when it bites a victim.

"As far as we can tell, *Bb* bacteria normally utilize blood as their main nutrient source, just as the tick does," said Dr. Michael Norgard, chairman of microbiology at UT Southwestern and senior author of the study. "When the tick is not feeding, and no nutrients are coming in, the bacteria are sort of in a quiescent state, waiting in the tick's midgut, which is equivalent to our digestive system."

When blood enters the tick gut, Dr. Norgard said it appears that changes in temperature and acidity signal the bacteria that the nutrient is present, triggering the bacteria to replicate in large numbers and migrate to the tick's salivary glands, where they are transmitted into animals or humans during the tick's feeding process. The energy for replication is believed to come from the proteins and nutrients made available as the tick breaks down whole blood.

"For some reason, bacteria lacking the BptA protein either can't utilize the blood meal in the way the wild-type bacteria do, or something about the blood becomes hostile to them," said Dr. Norgard. "Instead of helping the bacteria, the blood harms them. Ultimately, as the tick feeds on blood and begins to go through its molting process, the levels of the knockout *Bb* bacteria in the tick drop by about 90 percent, which is a very dramatic decrease."

In the study, each time infected ticks fed, bacteria levels within them dropped until they

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eventually were zero.

"We're not sure whether the lack of the BptA protein ultimately kills the bacteria or inactivates them," Dr. Norgard said. "But certainly it prevents them from replicating in the manner that they should to sustain the numbers needed to move from the midgut to the salivary glands. We don't understand the mechanism for that yet, and that will be the next step in our research."

Further study of the function of the BptA protein could give researchers additional clues as to how the organism has evolved to survive in ticks and why it has chosen a tick environment to be its natural vector in nature.

"It potentially could give us a target for eradicating the bacterium, because if you understand what it needs to sustain itself, then in theory you could disrupt that cycle by blocking whatever that mechanism is," Dr. Norgard said.

Traditionally, scientists studying pathogens have looked at genes that affect how the infecting organisms behave once inside a human host. What tends to get ignored, Dr. Norgard said, is the other side of the coin.

"This organism has to live half of its life cycle in a tick," he said. "There must be subsets of genes important to its survival there. If it can't exist in ticks, it can't maintain itself in nature and hence can't infect animals or humans."

UT Southwestern molecular microbiology graduate student Andrew Revel, a lead author of the study, found the *bptA* gene by screening a number of candidate genes he thought might be affecting the survivability of *Bb* within its hosts. The research team had hypothesized that the elimination of the gene would somehow impact the pathogenesis of Lyme disease in mammals, but they found no evidence of that. Knockout bacteria not only survived within mice, but also produced Lyme disease in the animals.

"That's when we began to look more in the tick," Dr. Norgard said. "It wasn't until we went through the later stages of tick feeding – allowing the ticks to feed on mice, waiting a couple of months for the tick to molt, then refeeding them – that we began to see the effect. Our results required a much more comprehensive assessment of the total life cycle of the bacterium, as opposed to just focusing on the mammalian infection, which is what many scientists tend to do."

Other UT Southwestern microbiology researchers involved in the study were Dr. Jon Blevins, a lead author and research fellow; Lori Neil, research associate; and Dr. Kayla Hagman, assistant professor. Researchers from Oklahoma State University College of Veterinary Medicine and from Spain also contributed. The research was supported by the U.S. Public Health Service and the National Institutes of Health.

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