Researchers discover molecular target for the bacterial infection brucellosis

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UC Davis scientists have uncovered a potential drug target for the development of an effective therapy against the debilitating, chronic form of the bacterial disease brucellosis, which primarily afflicts people in Mediterranean and Middle Eastern countries.

Brucellosis, which affects about 500,000 people worldwide each year, typically is caused by ingestion of unsterilized milk or close contact with body secretions from infected animals. Symptoms include intermittent or irregular fever of variable duration, headache, weakness, profuse sweating, chills, weight loss and generalized aching. It can also cause long-lasting or chronic symptoms such as recurrent fevers, joint pain and fatigue.

In a paper published online this week in the journal *Cell Host & Microbe*, the researchers reported that they have identified the cells that harbor the *B. abortus* bacteria during the persistent phase of the brucellosis. The cells, known as alternatively activated macrophages (AAMs), are a recently identified category of immune defense cells.

The researchers also determined that the biological pathway peroxisome proliferator activated receptor ?, abbreviated as PPAR?, is responsible for altering the metabolism of AAMs so that they supply *B. abortus* with the energy in the form of glucose that enables bacteria to survive and replicate and thereby sustain the chronic phase of the infectious disease. Other labs also have shown that PPAR? control a cell's metabolism.

"We found that PPAR? induces a metabolic shift in these cells that causes them to generate glucose," said Renee Tsolis, associate professor of medical microbiology and immunology at UC Davis who led the study.

"Starving the *B. abortus* bacteria by inhibiting the PPAR? pathway may be a new approach to eradicating the chronic, difficult-to-treat form of Brucellosis infection that usually occurs because antibiotic therapy was not used during the acute, or early, phase of the infection," said Tsolis.

Tsolis and her collaborators were the first to discover PPAR?'s role in brucellosis and to determine that AAMs harbor the bacteria during the chronic stage of the disease. The identification of the bacteria's niche is another important clue for the development of a more effective treatment, she said.

In a series of experiments, Tsolis and collaborators found that the gene encoding PPAR? is very active during chronic Brucellosis infection, but not during acute infection, and that the *B. abortus* bacteria did not survive in AAMs when deprived of glucose.

When the researchers inactivated the protein that normally transports glucose, the bacteria stopped reproducing, and the infection no longer was chronic, she said.

In mice infected with *B. abortus*, Tsolis and collaborators treated the animals with GW9662, a PPAR inhibitor. The researchers administered the inhibitor before the infection became chronic, or long lasting. The inhibitor significantly reduced the amount of AAMs and *B. abortus* bacteria in the mice.

"These results suggested that inhibition of PPARreduced the bacteria's survival by reducing the abundance of AAMs during chronic infection,"

said Tsolis.

Conversely, when the researchers treated the *B. abortus*-infected mice with Rosiglitazone, a drug that boosts PPAR activity, the bacteria increased by two-fold during the acute phase and four-fold during the chronic phase of infection. Rosiglitazone and other drugs that boost PPARare used to treat type 2 diabetes because they lower blood glucose by increasing cellular glucose uptake.

In other experiments, the researchers showed that AAMs, one of two categories of macrophages, are abundant in the spleen during chronic brucellosis but not during the acute, or initial, phase of the infection, which is dominated by classically activated macrophages (CAM), the second category of these immune cells.

In addition to profuse sweating, symptoms of brucellosis infection include joint and muscle pain. Among the complications of chronic infection are arthritis and endocarditis, a serious inflammation of one of the four heart valves. Brucellosis rarely occurs in the U.S., with about 100 to 200 cases reported each year, according to the U.S. Centers for Disease Control and Prevention.

More information: The title of the journal paper is "A PPAR?-mediated increase in glucose availability sustains chronic Brucella abortus infection in alternatively activated macrophages."

Provided by UC Davis