Trudeau Institute reports new approach to treating Listeria infections

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Research underway at the Trudeau Institute could lead to new treatments for people sickened by Listeria and other sepsis-causing bacteria. Dr. Stephen Smiley's laboratory has published a study in the scientific journal *Infection and Immunity* that supports a new approach to treating these infections.

Listeria can cause serious illness, especially among the elderly, the very young and those with compromised immune systems. The bacteria can also cause significant complications in pregnant women, including miscarriage.

The CDC is reporting that one miscarriage and 23 deaths can be attributed to a recent outbreak of Listeria infections in the United States caused by tainted cantaloupes; 116 persons from 25 states have been infected with the outbreak-associated strains.

Ingestion of Listeria usually causes a limited gastrointestinal illness; however, the bacteria sometimes spread to other parts of the body, resulting in a deadly sepsis. Despite decades of medical research, severe infections caused by Listeria and other bacteria that cause sepsis, like MRSA, still threaten human health.

The Trudeau Institute study demonstrates that mice that have been genetically modified so they cannot produce factor XI (FXI), a specific blood-clotting factor, have an improved capacity to withstand injection with high doses of Listeria. The study also shows that normal mice

treated with both an antibody targeting FXI along with antibiotics show improved survival during septic Listeria infection, as compared with mice treated with antibiotics alone.

These findings suggest FXI-targeted therapeutics may be useful for treating severe infections caused by Listeria and other sepsis-causing bacteria.

This recent work builds on a long history of Listeria research at the Trudeau Institute. In the 1960s the Institute's first director, Dr. George B. Mackaness, advanced the use of mouse models to study how cells of the immune system combat Listeria. He discovered that activated macrophages play a critical role in killing Listeria. He also discovered that lymphocytes, another type of immune cell, orchestrate this killing response. These seminal observations remain the foundation for modern studies of cell-mediated defense against pathogens.

The Trudeau Institute's second director, Dr. Robert J. North, extended this work by identifying the key subset of anti-Listeria lymphocytes: T cells. Dr. North and his Trudeau colleagues also described crucial roles for NK cells and neutrophils.

Several years ago, Dr. Smiley discovered that blood-clotting proteins also play critical protective roles during immune defense against Listeria. "I was really intrigued by our finding that clotting protects against Listeria because so many other studies had shown that clotting clogs blood vessels and contributes to organ failure and death during septic infections," said Dr. Smiley.

"Our finding suggested that some degree of blood clotting is essential for effective immune defense, but too much is harmful. We set out in search of ways to prevent the bad clotting while maintaining the good."

Specifically, Dr. Smiley's lab looked for clotting factors that appeared to be hyperactive in the septic state.

"The paper we've just published is our first demonstration of this exciting new approach to treating sepsis – we found that FXI is overproduced during septic Listeria infections and that therapeutics targeting FXI can reduce septic disease while maintaining immune defense."

Provided by Trudeau Institute