Fruit flies show how salmonella escapes immune defenses

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Salmonella are wily and obnoxious bacterial invaders--escape artists capable of evading multiple immune responses and causing a harsh and debilitating intestinal infection.

Researchers have come closer to understanding how these bacteria manage to thwart two major categories of immune defenses at once and set up shop in a host organism. New results are reported in the April 2008 issue of the journal *Cell Host & Microbe*.

The Emory University research team used a transgenic fruit fly (drosophila) model to test a group of "effector proteins," also known as "virulence factors," secreted by invading organisms to usurp the host immune response for their own benefit.

They found that one of these proteins, named AvrA, not only shuts down the key immune signaling pathways JNK and NF-kB, but also turns off the fail safe system organisms have evolved to respond to irreversible threats. This ultimate immune defense, called apoptosis, eliminates invaders along with the infected cells through a system of programmed cell death.

In previous research, the scientists had showed that AvrA could suppress some aspects of immune system signaling in cell culture, but they wanted to study the protein in a whole animal system.

"Bacterial proteins are notoriously difficult to study," says Andrew

Neish, MD, Emory professor of pathology and laboratory medicine and the study's lead scientist. "Using the drosophila system allowed us to express bacterial proteins in a controlled fashion. We were able to study salmonella infection and the associated proteins and signaling mechanisms in a whole animal, which gave us information we could not have gained from a cell culture dish."

To evaluate the effects of AvrA in natural salmonella infection in mammals, the scientists used a mouse model of salmonella infection and found that AvrA suppressed the same immune signaling pathways and apoptotic reaction as in the drosophila model. A mutant form of the salmonella lacking the AvrA protein caused an enhanced inflammatory immune response and markedly more cell death in the mouse intestine.

"Using drosophila genetics, we found a biochemical crossroad required for both immune and apoptotic pathways," says Neish. "The AvrA protein is able to key in on the exact site of the biochemical network and allow it to suppress both the inflammatory response and the apoptotic immune response at the same time. We suspect that other pathogens may target the same biochemical network to avoid elimination. These immune pathways in drosophila have been preserved across evolution and are remarkably similar to human immune pathways. This is such a powerful research system that any bacterial or viral genes would be amenable to study through this approach."

Source: Emory University