UT SOUTHWESTERN MEDICAL CENTER NEWS

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Cannibalistic cells may help prevent infections, UT Southwestern researchers report

DALLAS – Aug. 3, 2009 – Infectious-disease specialists at UT Southwestern Medical Center have demonstrated that a cannibalistic process in cells plays a key role in limiting *Salmonella* infection.

Salmonella, the causative agent of salmonellosis, causes many of the intestinal infections and food-related illnesses reported in the U.S. About 600 people die each year as a result of these infections, accounting for roughly 30 percent of all reported food-related deaths. It is particularly dangerous among the elderly.

The new findings, available online and in an upcoming issue of the *Proceedings of the National Academy of Sciences*, are among the first to demonstrate that a process called autophagy (pronounced "aw-TAH-fah-gee") prevents harmful bacteria such as *Salmonella* from becoming successful pathogens. The findings also suggest that decreases in autophagy – such as those that occur in the elderly and in certain patients with Crohn's disease, an inflammatory bowel disorder – may lead to abnormalities in the way the intestinal tract deals with bacterial infections.

"It's known that as you get older you become more susceptible to infectious diseases and also that autophagy decreases," said Dr. Beth Levine, chief of the division of infectious diseases at UT Southwestern and senior author of the new study in *PNAS*. "In this paper, we've shown that signaling pathways that extend life and protect against bacterial invaders do so by triggering autophagy. This suggests that therapeutic strategies to increase autophagy may be effective in defeating harmful bacteria that can enter inside cells."

Autophagy is the way cells devour their own unwanted or damaged parts. It is a highly regulated and completely normal process by which cells remain healthy by performing "routine housekeeping" and "garbage disposal." Prior research has shown that the process appears to be an adaptive response that our bodies employ during times of stress or starvation, and which also helps protect our bodies against cancer and neurodegenerative diseases.

It's unclear why older people become more susceptible to infections, but research has shown that autophagy does decrease with age. Dr. Levine, a professor of internal medicine and

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microbiology, said it is possible that by reversing or regulating this process, researchers could prevent the elderly and others with weakened immune systems from becoming more susceptible to infections.

For this study, the researchers studied the effects of *Salmonella* infections in two organisms they had genetically engineered to lack active autophagy genes. The organisms included *Caenorhabditis elegans*, a common research worm also known as a nematode, and *Dictyostelium discoideum*, a soil amoeba that functions much like certain cells in the human immune system.

In both cases, the animals with inactive autophagy genes fared far worse than those with active ones. Rather than being targeted for elimination, the *Salmonella* bacterium was able to invade the host cells, where it started replicating, Dr. Levine said.

She said the findings indicate that the autophagy process plays an important role in resistance to certain types of pathogens, specifically those that can enter inside our cells.

The next step, Dr. Levine said, is to begin studying the efficacy of a new autophagy-inducing molecule in treating a number of intracellular bacterial infections including salmonellosis, tuberculosis, tularemia and listeriosis.

Other UT Southwestern researchers involved in the study were Dr. Kailiang Jia, lead author and instructor in internal medicine; Dr. Muhammad Akbar, clinical instructor in internal medicine; Dr. Qihua Sun, research scientist in internal medicine; Beverley Adams-Huet, assistant professor of clinical sciences; Dr. Christopher Gilpin, assistant professor of cell biology; and Dr. Collin Thomas, a former research associate in internal medicine.

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