Genetically engineered Salmonella promising as anti-cancer therapy

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A new study has demonstrated that genetically modified *Salmonella* can be used to kill cancer cells. The study is published in this week's issue of *mBio*, an American Society for Microbiology online-only, open access journal.

"There has long been interest in using genetically engineered microbes to target and destroy cells within solid tumors. I think this study goes a significant way in developing some strategies that will help in the overall means of using *Salmonella* as part of a cancer therapy," said Roy Curtiss, III, PhD, who was involved with the research. Dr. Curtiss is University Professor of Microbiology and Director, Center for Infectious Diseases and Vaccinology and Center for Microbial Genetic Engineering, the Biodesign Institute, Arizona State University.

For years, researchers have known that certain strains of bacteria, including *Salmonella enterica*, can kill cancer cells. Specifically *Salmonella enterica* Serovar Typhimurium has been shown to not only colonize solid tumors, but also to exhibit an intrinsic antitumor effect. However, in order to use *Salmonella* as a weapon against cancer in humans, researchers must find a balance between allowing it to kill the cancer and be safe for the patient. The bacteria, commonly known for causing severe food poisoning, can lead to sepsis and death in humans.

In the new study, the researchers focused on modifying the lipopolysaccharide structure (LPS) of the *Salmonella* strain to make the bug less toxic. LPS, found in the outer membrane of bacteria, is one of

the major inducers of sepsis, a life-threatening infection. The researchers used genetic engineering to delete genes involved in the synthesis of the LPS, and then tested various modified *Salmonella* strains to see how they performed in test tube studies with human cancer cells and in tumor bearing mice. They identified a particular mutant strain that was the most effective at killing cancer cells and shrinking tumors, and also unable to cause disease. However, this mutant strain was less able to colonize the tumors, although being most effective in killing tumor cells when getting there.

To address this problem, the researchers then added another genetic modification, an inducible arabinose promoter. The modification allowed the *Salmonella* to be injected in the mouse in a form that would not harm normal, healthy cells, was effective at colonizing tumors, and after entering cancer cells, would turn toxic. "This transition from a benign, invasive *Salmonella* that doesn't hurt normal cells to the toxic type occurs very rapidly (time wise) in the tumor due to the very rapid growth and cell division that occurs when *Salmonella* enters a tumor," said Dr. Curtiss. In a normal cell, *Salmonella* grows very slowly, dividing once or twice in a 24-hour period, but in a tumor, the bacteria divide every hour.

According to Dr. Curtiss, the investigational therapy would probably be used in conjunction with chemotherapy and radiation therapy, once it gets to human trials.

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