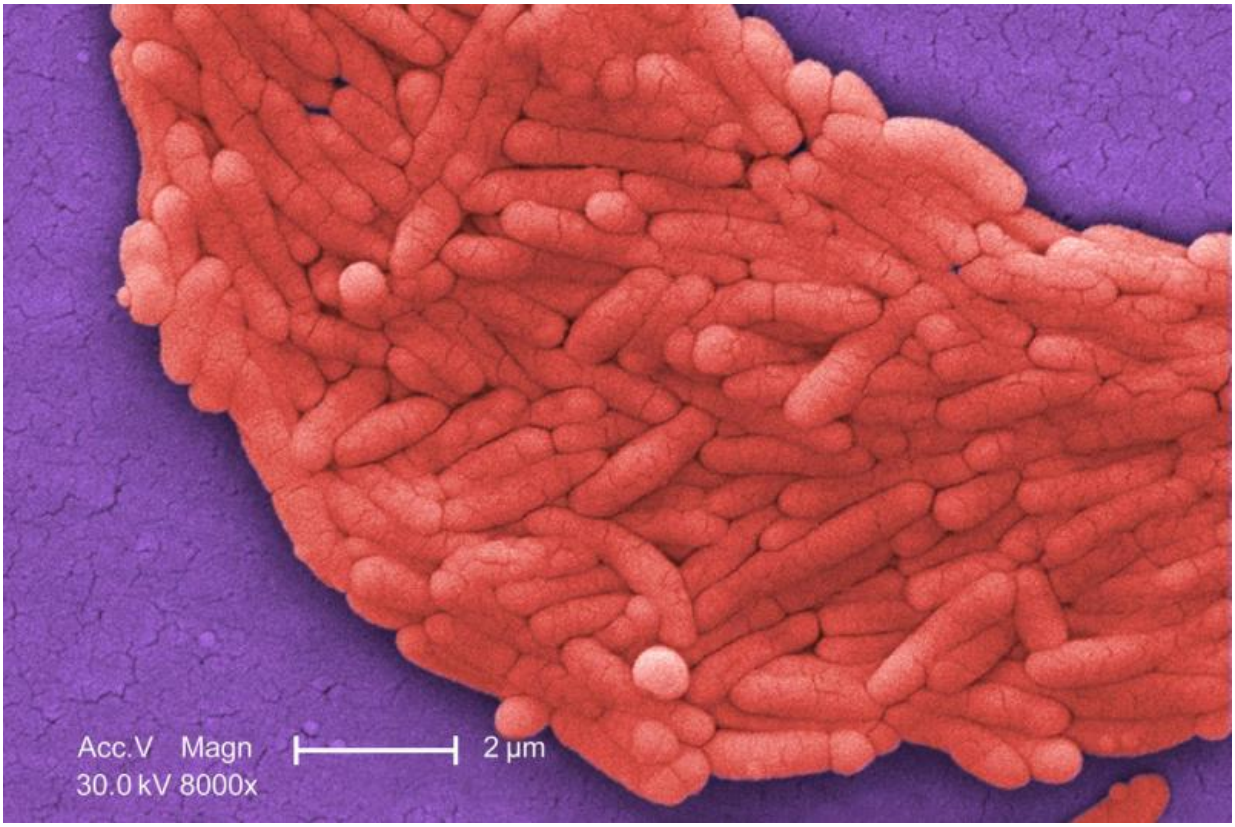
Genetically altered bacteria help destroy cancerous tumors in mice

February 9 2017, by Bob Yirka



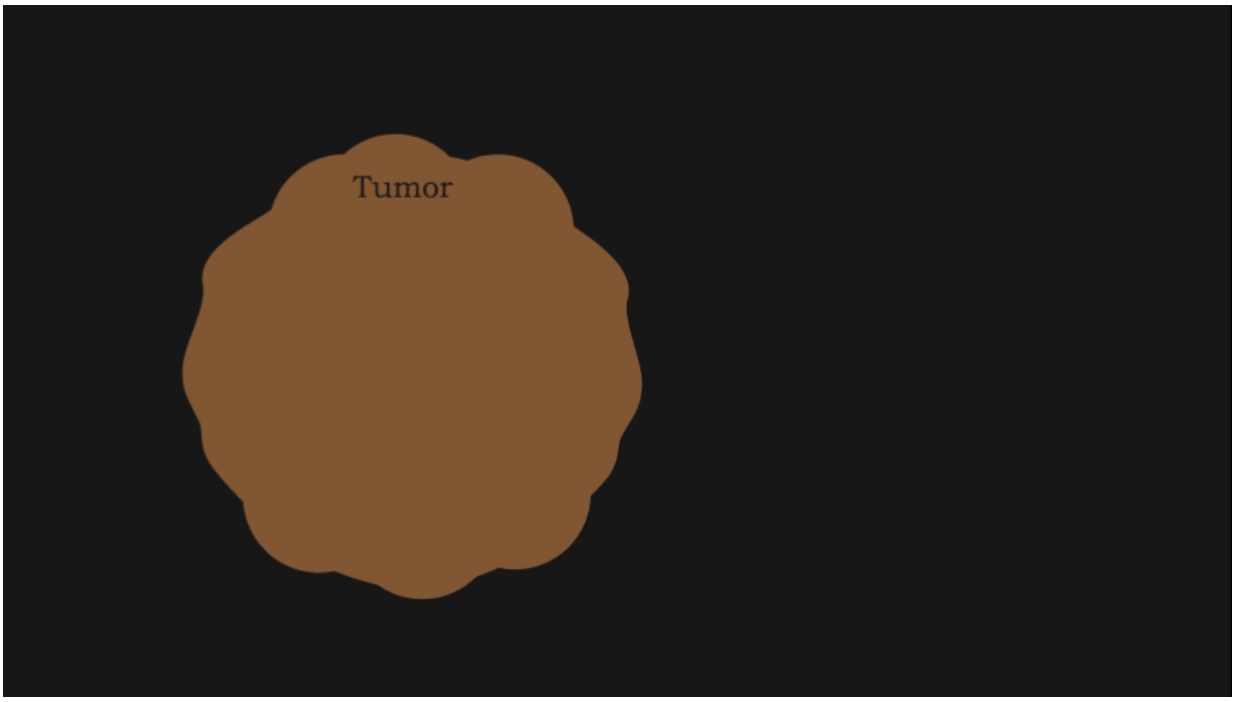
Salmonella forms a biofilm. Credit: CDC

(Medical Xpress)—A team of researchers affiliated with multiple institutions in Korea has found that genetically altering a type of bacteria and injecting it into cancerous mice resulted in the disappearance of

tumors in more than half of test mice. In their paper published in the journal *Science Translational Medicine*, the researchers describe how they came upon the idea of altering a common type of bacteria to see if it might help fight cancer and the results of their tests.

The researchers report that they were working on two projects—developing a vaccine against a type of bacteria that was infecting shellfish and testing bacteria as a means for fighting cancer. They noticed that the bacteria that attacked shellfish produced a protein (FlaB) that caused a strong immune response. That led them to genetically modify the common salmonella bacteria so that it, too, would produce the protein. Salmonella, by its very nature, tends to seek out oxygen-poor tissue and kill it, which is why it has been studied as a tumor fighter—tumors are naturally oxygen-poor environments. But while releasing salmonella into the bloodstreams of cancer-stricken mice has resulted in reduction of tumor size, the result was temporary—the tumors returned. This, the researchers believed, was due to the tumors not being completely eradicated. In this new effort, they added a second element to such attacks to help kill off some tumors completely.

The researchers found that their genetically modified salmonella made its way to several organs in the bodies of mice and also into tumors. The immune system then successfully eradicated the bacteria from the organs while simultaneously attacking the bacteria in the tumors and by extension the tumors themselves. This approach proved successful—11 out of 20 mice were tumor free after 12 days.



Engineered bacteria target tumors and activate the host immune system to eliminate cancer cells. Credit: Carla Schaffer / Zheng et al. / *Science Translational Medicine*

The researchers then embarked on another experiment—first transplanting metastasizing cancer cells into test mice and then injecting them with genetically altered bacteria and waiting to see what would happen. After 27 days, the researchers found that four out of eight mice had four or fewer tumors and some had none at all—meanwhile, all of the mice in a control group were found to have dozens of new tumors.

More information: Jin Hai Zheng et al. Two-step enhanced cancer immunotherapy with engineeredsecreting heterologous flagellin, *Science Translational Medicine* (2017). DOI: 10.1126/scitranslmed.aak9537

Abstract

We report a method of cancer immunotherapy using an attenuated Salmonella typhimurium strain engineered to secrete Vibrio vulnificus flagellin B (FlaB) in tumor tissues. Engineered FlaB-secreting bacteria effectively suppressed tumor growth and metastasis in mouse models and prolonged survival. By using Toll-like receptor 5 (TLR5)–negative colon cancer cell lines, we provided evidence that the FlaB-mediated tumor suppression upon bacterial colonization is associated with TLR5-mediated host reactions in the tumor microenvironment. These therapeutic effects were completely abrogated in TLR4 and MyD88 knockout mice, and partly in TLR5 knockout mice, indicating that TLR4 signaling is a requisite for tumor suppression mediated by FlaB-secreting bacteria, whereas TLR5 signaling augmented tumor-suppressive host reactions. Tumor microenvironment colonization by engineered Salmonella appeared to induce the infiltration of abundant immune cells such as monocytes/macrophages and neutrophils via TLR4 signaling. Subsequent secretion of FlaB from colonizing Salmonella resulted in phenotypic and functional activation of intratumoral macrophages with M1 phenotypes and a reciprocal reduction in M2-like suppressive activities. Together, these findings provide evidence that nonvirulent tumor-targeting bacteria releasing multiple TLR ligands can be used as cancer immunotherapeutics.