Molecular switch lets salmonella fight or evade immune system

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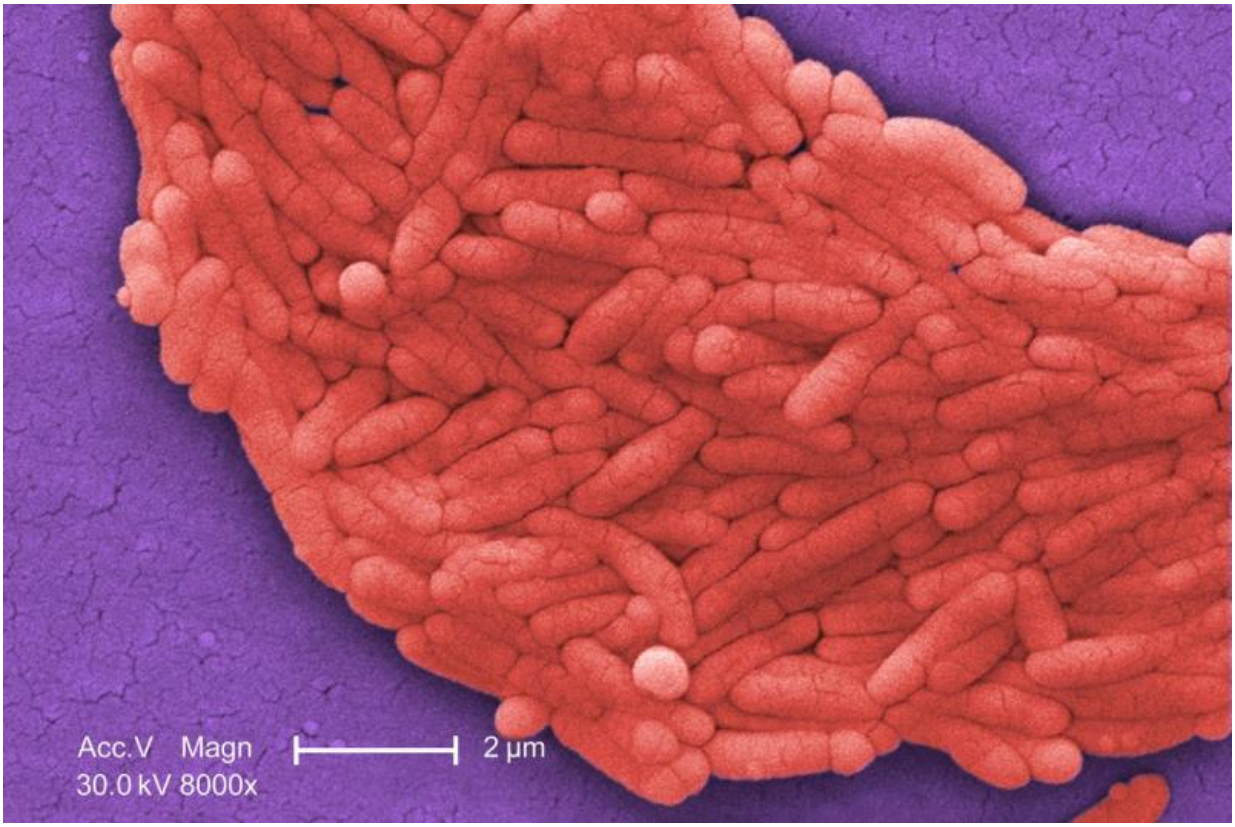

Salmonella forms a biofilm. Credit: CDC

Researchers at the University of Illinois at Chicago have discovered a molecular regulator that allows salmonella bacteria to switch from actively causing disease to lurking in a chronic but asymptomatic state

called a biofilm.

Their findings are published in the online journal, *eLife*.

Biofilms cling to surfaces in the body, such as the bronchial tubes or artificial joints, often without causing illness. But they can be a reservoir of bacteria that detach and cause disease or infect new hosts. The biofilms are resistant to host defenses and antibiotics because their tightly-packed structure exposes little surface area for drugs to reach. Many pathogenic bacteria are able to switch from an infectious to a dormant state as a strategy for survival inside their hosts.

Linda Kenney, professor of microbiology and immunology at the UIC College of Medicine and lead author of the study, had been studying how salmonella survive inside immune system cells called macrophages. These white blood cells patrol the body and engulf viruses and bacteria they encounter. They encase their prey in a bubble called a vacuole that protects them from the invader until it can be destroyed.

Macrophages digest their quarry when the acidity inside the vacuole drops in response to the captive. But the bacteria have evolved a unique defense, enabling them to survive inside the vacuole and use the macrophage as a Trojan horse to travel elsewhere in the body undetected by other immune cells.

Kenney knew that a type of salmonella that causes typhoid fever in humans, called *Salmonella typhi*, and its mouse counterpart, *Salmonella typhimurium*, were able to survive inside macrophage vacuoles. She noticed that these bacteria did two things: inside the vacuole, they formed a kind of syringe - a long, hollow filament to inject the vacuole with a host of proteins that altered it. They also quickly assumed the same acidity of the vacuole.

"These two defenses, together, allow salmonella to survive and replicate in the harsh conditions of the vacuole," Kenney said.

Further experiments revealed that sensing and mirroring the acidity, or pH, of the vacuole is what triggers salmonella to form the syringe.

"The syringe-forming and pH-adjusting genes are signaled to turn on by the lower pH inside the vacuole," Kenney said. But these same salmonella, equipped to survive the hostile environment inside a macrophage vacuole, were also able to exist free in the body of the host—as biofilms.

"I wanted to know how Salmonella 'decide' between these two very different lifestyles," Kenney said.

Studying S. typhimurium, Kenney discovered that the molecular switch is a bacterial molecule called SsrB. As the macrophage vacuole starts to acidify, SsrB is activated and it turns on the genes needed to form the syringe and adjust the pH. When salmonella lives outside the vacuole, where pH levels are neutral, SsrB instead turns on genes for sticky proteins in the membrane that help bacteria bind to one another to form biofilms.

Kenney said that many disease-causing salmonella evolved from harmless strains partly by acquiring new genes from other germs in a process called horizontal gene transfer.

"Salmonella acquired their pH-adjusting and syringe-forming genes in this way, as well as the switch that turns them on and off - SsrB," she said. "The default mode, or its ancestral program, dictates that it make biofilms, cause no illness, and survive long enough to infect new hosts when the opportunity arises. The new genes allow it to survive the host's main defense—the acidifying macrophage vacuole."

Understanding how bacteria switch from the disease-causing state to the biofilm state could help scientists develop anticancer drugs that encourage the formation of biofilms on tumors, Kenney said.

"When salmonella forms biofilms on tumors, it releases TNF-alpha, a powerful anti-tumor molecule," she said. "If we can better control the formation of biofilms, we can target them to tumors for cancer therapy."

More information: The horizontally-acquired response regulator SsrB drives a Salmonella lifestyle switch by relieving biofilm silencing, dx.doi.org/10.7554/eLife.10747 , elifesciences.org/content/5/e10747

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