Researchers identify the secret genetic weapon of Clostridium difficile

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A trio of researchers at the University of Texas Health Science Center, School of Public Health in Houston, have identified the location of the genes that control production of toxins that harm people infected by *Clostridium difficile* bacteria. The gene locus, agr1, forms part of a signaling communication system that produces a small molecule that, in turn, tells the rest of the population to turn on their toxin genes.

Clostridium difficile causes severe diarrheal diseases by producing toxins; the most virulent are known as Toxin A and Toxin B. Study leader and molecular microbiologist Charles Darkoh, who has been studying this bacterium since 2007,says researchers did not previously know the role of agr1 in C.difficile infections, or CDIs. His group's findings, which combined genetic analysis of *C. difficile* with experiments on mice, suggest a new way to treat the disease, by jamming this signaling communication system and stopping toxin production.

C. difficile resists most of the available antibiotics. "It has become important to develop a non-antibiotic therapy for this life-threatening infection," says Darkoh. "We have uncovered a pathway that we and other researchers can target to develop a non-antibiotic therapy for *C. difficile* infections".

C. difficile ordinarily live in the intestines - of humans, as well as animals - as one of many non-harmful bacterial species. But when a person undergoes long-term antibiotic therapy, the medicine can wipe out helpful bacterial species that keep *C. difficile* in check. As a result, the bacteria flourish, producing toxins and causing problems. Some people experience only mild symptoms; for others, it's fatal. The infection causes a variety of dangerous diarrheal diseases and toxic megacolon. People in hospitals and long-term care facilities face the highest risk of infection. In 2011, according to the Centers for Disease Control and Prevention, CDIs caused nearly 500,000 infections and killed about 29,000 people.

CDIs are notoriously difficult to treat and infections have increased in severity and number since the beginning of the 21st century, especially among older patients. Doctors typically prescribe one of the three antibiotics, but patients become resistant to those treatments. Infections recur in as many as 25 or 30 percent of cases. Darkoh says *C. difficile* infection is a public health problem and finding a non-antibiotic method of treating CDIs is critical to public health.

"Bacteria always find a way to survive when they are under pressure to die,"says Darkoh. He is currently developing an oral drug that wouldn't kill the bacteria. Instead, it would inactivate the toxins and cripple the toxin-making machinery of *C. difficile* by targeting the pathways regulated by agr1.

Last year, in a related study published in *mBio*, Darkoh and his collaborators identified the accessory gene regulator (Agr) quorum signaling system as responsible for controlling synthesis of the toxins. The new study builds on that work by identifying culpable genes within the system.

The researchers began by investigating agr1 and agr2, two gene loci associated with the Agr signaling system. Agr1 appears in the genomes of every sequenced strain of *C. difficile*, while agr2 does not. Next, they found that mice infected with a *C. difficile* mutant whose agr1 locus had been deleted did not produce toxins or cause disease, even though the bacterium still colonized the animal intestines. Darkoh says agr2 is not related to the toxins, and he plans to report on its role in a future publication.

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