Research identifies new way to treat common hospital-acquired infection

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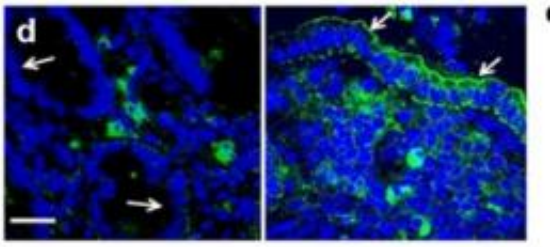

The right image shows abundant S-nitrosylation (green) in human colitis compared with much less found in the left image of a normal colon. Credit: UCLA/University of Texas Medical Branch at Galveston

Researchers at the David Geffen School of Medicine at UCLA and the University of Texas Medical Branch at Galveston have discovered a molecular process by which the body can defend against the effects of Clostridium difficile infection (CDI), pointing the way to a promising new approach for treating an intestinal disease that has become more common, more severe and harder to cure in recent years.

In the U.S., several million people are infected each year, approximately double the incidence of a decade ago, mainly due to the emergence of a new, highly virulent strain of the bacteria that causes CDI.

As a result of the study findings, published in the Aug. 21 online edition of the journal Nature Medicine, the researchers are preparing to launch

clinical trials using their discovery as a new CDI therapeutic approach. The team also included researchers from Case Western Reserve University, Tufts University and the Commonwealth Medical College.

CDI is a bacterial infection that can cause diarrhea and more serious intestinal conditions, such as colitis, the inflammation of the colon. In the most severe cases, CDI can be fatal. It is most commonly acquired in hospitals by patients, particularly the elderly, who are being treated with antibiotics for another infection.

Currently, one of two potent antibiotics is used to treat the infection, but up to 20 percent of patients experience a relapse and a return of symptoms within a few weeks.

"We are treating a disease caused by antibiotics with yet another antibiotic, which creates the conditions for re-infection from the same bacteria," said study co-author Dr. Charalabos Pothoulakis, director of UCLA's Inflammatory Bowel Disease Center and a professor of medicine in the division of digestive diseases. "Identification of new treatment modalities to treat this infection would be a major advance."

Clostridium difficile causes diarrhea and colitis by releasing two potent toxins into the gut lumen that bind to intestinal epithelial cells, initiating an inflammatory response. These toxins are released only when the Clostridium difficile bacteria are multiplying. When antibiotics are used to treat another infection, it changes the bacterial landscape in the gut and, in the process, may kill bacteria that under normal conditions would compete with Clostridium difficile for energy. Scientists believe this may be what provides the opportunity for Clostridium difficile to grow and release its toxins.

The UCLA and University of Texas researchers found in laboratory studies that upon infection with Clostridium difficile, human cells in the

gut are capable of releasing molecules that will neutralize these toxins, rendering them harmless. In animal studies, the researchers showed that using a drug to induce this process, known as protein s-nitrosylation, inhibited Clostridium difficile toxins from destroying intestinal cells. Forthcoming clinical trials will test this approach in humans.

"Our study suggests a novel therapeutic approach for treating Clostridium difficile infection by exploiting a newly discovered defense mechanism that has evolved in humans to inactivate microbial toxins," said Tor C. Savidge, an associate professor in the division of gastroenterology and hepatology at the University of Texas Medical Branch at Galveston and the paper's lead author.

Along with its potential to provide a much-needed new approach to treating CDI, the discovery could be applied to developing new treatments for other forms of diarrhea, as well as non-diarrheal diseases caused by bacteria.

"We already know through gene-sequencing analysis that hundreds of microbial proteins can be regulated by s-nitrosylation," Pothoulakis said. "If we are successful with this approach, we may be able to treat other bacterial diseases in a similar way."

Provided by University of California - Los Angeles