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C. Difficile Researchers Reveal Potential Target to Fight Infections

Researchers have discovered how *Clostridium difficile*, a common germ in healthcare-associated infections, sends the body's natural defenses into overdrive, actually intensifying illness while fighting infection.

The discovery at Virginia Bioinformatics Institute at Virginia Tech in the US, which was recently published in PLOS One, may lead to new drug treatments for *C. difficile*. The bacterium has been linked to the death of 14,000 Americans annually, according to the Centers for Disease Control and Prevention.

Researchers with the Center for Modeling Immunity to Enteric Pathogens at Virginia Tech applied computational and mathematical modeling in combination with RNA-sequencing and mouse studies to understand an important regulatory pathway during *C. difficile* infection.

The human intestine must peacefully coexist with trillions of beneficial bacteria while quickly responding to pathogens such as *C. difficile*. Sometimes the immune system will go into overdrive when responding to such pathogens and in the attempt to clear infection more damage is caused. "We have found that tissue damage and disease severity in *C. difficile* infection is associated with a disruption of the peroxisome proliferator-activated receptor gamma (PPARγ) pathway," said Professor Josep Bassaganya- Riera, director of the Nutritional Immunology and Molecular Medicine Laboratory, and the principal investigator with the Center for Modeling Immunity to Enteric Pathogens.

When studying the bowels of mice, researchers found that the PPAR γ pathway keeps the immune response in check, allowing the body to heal while the immune cells that fight infection do their work in a controlled manner. When PPARγ was absent or inactive, disease was more rampant and colonic lesions from *C. difficile* were much worse.

In addition, researchers found that by using an existing diabetes drug the protective mechanism could be activated and the severity of the *C. Difficile* infection could be reduced. More studies will be needed before the drug can be tested against *C. difficile*.

"This research demonstrates that the integration of powerful computer simulations of host responses with immunology experimentation not only contributes to a better understanding of the immunoregulatory processes in the gut mucosa during *C. difficile* infection, but it also advances the discovery of broad-based therapeutic targets in the host for infectious diseases," said Raquel Hontecillas, assistant professor of immunology at Virginia Tech, co-director of the Nutritional Immunology and Molecular Medicine Laboratory and leader of the immunology component of the Center for Modeling Immunity to Enteric Pathogens.

This research builds on previous work from the Nutritional Immunology and Molecular Medicine Laboratory, which shows that PPAR γ is critical to reducing disease caused by enteric pathogens and regulating autoimmune diseases such as inflammatory bowel disease.

C. difficile has become a widespread problem in hospitals, particularly with patients who have received heavy doses of multiple antibiotics, and the problem continues to spread in the community, increasingly being found in patients who traditionally would not be susceptible to this bacterium. Symptoms include persistent diarrhea, fever, gut inflammation, and weight loss.

Current strains of *C. difficile* have become even more virulent and antimicrobial resistant in recent years, which emphasises the importance of developing broad-based, host-targeted approaches to control the disease as opposed to just relying on anti-microbial therapies that target the bacterium and can stimulate the spread of resistance.

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