C. diff scientists reveal potential target to fight infections

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Researchers at Virginia Bioinformatics Institute at Virginia Tech have discovered how a common diarrhea-causing bacterium sends the body's natural defenses into overdrive, actually intensifying illness while fighting infection.

The discovery, recently published in *PLOS One*, may lead to new drug treatments for Clostridium difficile, a common germ in health care-associated infections often referred to as C. diff. It 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 Clostridium difficile infection.

"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 Josep Bassaganya-Riera, a professor of immunology, director of the Nutritional Immunology and Molecular Medicine Laboratory and the principal investigator with the Center for Modeling Immunity to Enteric Pathogens.

The human intestine must peacefully coexist with trillions of beneficial

bacteria while swiftly responding to pathogens such as C. difficile. Sometimes the immune system will go into overdrive when responding to pathogens, causing more damage in an attempt to clear the infection.

Scientists studying mice bowels found the PPARγ 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 the protective mechanism can be activated and the severity of the C. difficile infection can be reduced by using an existing diabetes drug. 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, an 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 PPARγ is critical to reducing disease caused by enteric pathogens and regulating autoimmune diseases such as inflammatory bowel disease.

"With continued research, new drugs targeting this pathway will be developed that will have fewer side effects and greater efficacy than those currently on the market," Bassaganya-Riera said.

C. difficile has become a widespread problem in hospitals with patients who have received heavy doses of multiple antibiotics and it is spreading in the community. Symptoms include persistent diarrhea, fever, gut inflammation, and weight loss. Even though such potentially life-threatening intestinal infections occur among very young, elderly or immune-compromised individuals, C. difficile has increasingly been found in patients who traditionally would not be susceptible to this bacterium.

Current strains of C. difficile have become even more virulent and anti-microbial resistant in recent years which emphasizes 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.

More information: Viladomiu M, Hontecillas R, Pedragosa M, Carbo A, Hoops S, et al. (2012) Modeling the Role of Peroxisome Proliferator-Activated Receptor γ and MicroRNA-146 in Mucosal Immune Responses to Clostridium difficile. PLoS ONE 7(10): e47525. doi:10.1371/journal.pone.0047525

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