Math model of colon inflammation singles out dangerous immune cells

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Scientists at the Virginia Bioinformatics Institute (VBI) at Virginia Tech have constructed a mathematical and computational model of inflammatory bowel disease that allows researchers to simulate the cellular and molecular changes underlying chronic inflammation in humans. The model allows scientists to explore different interactions of cells in the immune system, check how these cells are linked to inflammation in the colon, and identify intervention points to perhaps stop the disease in its tracks. The work appears in the *Journal of Theoretical Biology*.

More than 1 million people are affected by inflammatory bowel disease in North America alone and direct healthcare expenses for inflammatory bowel disease in the United States are estimated at more than $15 billion annually. What the scientists have been able to do is construct a set of mathematical equations that describe the movement of different cells in the immune system and how these cells interact with different bacteria that can trigger disease in the colon.

Said Josep Bassaganya-Riera, associate professor at VBI, "In collaboration with the Network Dynamics and Simulation Science Laboratory at VBI, researchers in the Nutritional Immunology and Molecular Medicine group have developed a model of inflammation that allows us to investigate in silico the immunological changes that occur when inflammatory bowel disease takes hold of otherwise healthy gastrointestinal tissue."

Inflammatory bowel disease starts when the gut initiates an abnormal immune response to some of the one hundred trillion or so bacteria that come into contact with the colon of the human body. In some cases, this response can lead to inflammatory lesions and ulcerations in the cells lining the colon through which bacteria can invade the tissue. This invasion can lead to recurring inflammation, diarrhea, rectal bleeding, and malnutrition, the tell-tale symptoms of inflammatory bowel disease and infections with some gastroenteric pathogens.

Said Stephen Eubank, deputy director of the Network Dynamics and Simulation Science Laboratory at VBI and one of the authors on the paper, "One thing we are trying to understand with this research is how your immune system lives in peace with the commensal, peace-loving bacteria, yet can still mount a rapid, controlled defense against unfriendly bacteria. We are also interested in what happens when parts of the immune system do not behave as expected, for example when otherwise friendly immune cells attack healthy tissue." Remarked Eubank: "The computational model described in this paper allows scientists to examine these types of events in considerable detail but we are already working on a next-generation model that will allow us to take an even bigger step. Our goal is to develop an agent-based model in a petascale computing environment that will be able to represent hundreds of millions of cells involved in this type of immune response."

Previous studies have shown that in healthy individuals the detrimental immune response is avoided by the presence of regulatory immune cells that inhibit the inflammatory pathway. Added Bassaganya-Riera, "Our model allows researchers to identify those components of the inflammatory pathway that allow regulatory mechanisms to be overridden and immune-mediated disease to proceed."

The mathematical and computational approach of the scientists has already revealed one of the weak links in the complex network of

interactions. Said Katherine Wendelsdorf, a graduate student in the Network Dynamics and Simulation Science Laboratory at VBI and lead author of the paper, "Our math analyses revealed a specific type of immune cell, a pro-inflammatory macrophage, to be one of the main culprits for unregulated inflammation in inflammatory bowel disease."

When conditions were simulated in which M1 or classically activated macrophages were removed from the site of infection, a drastic decrease in the inflammatory response linked to disease was observed in the simulations. This observation suggests that M1 macrophages are key targets for intervention strategies to fight mucosal inflammation.

Said Bassaganya-Riera, "Modeling approaches cannot replace experimentation but they can provide a framework for organizing existing data, generating novel mechanistic hypotheses and deciding where to focus key validation experiments. Future efforts in our group will focus on modeling immunity to enteric pathogens."

More information: Wendelsdorf K, Bassaganya-Riera J, Hontecillas R, Eubank S (2010) Model of colonic inflammation: Immune modulatory mechanisms in inflammatory bowel disease Journal of Theoretical Biology 264(4): 1225-1239.

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