How mucosal infections can rewire an immune response to shape susceptibility to recurrence

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Scientists have shed new light on how mucosal infections can affect the body's inflammatory response to shape susceptibility to recurrence.

Their study in mice reveals how recurrent mucosal infections, specifically bladder infections, can rewire inflammatory responses driven by a protein called tumor necrosis factor-alpha (TNFα) to impact susceptibility. The findings, published in *eLife*, could inform the development of effective new treatment strategies.

Mucosal bacterial infections, which include urinary tract infections (UTIs), are common. In the US alone, they account for over 42m outpatient visits and most of the 270m antibiotic prescriptions given to outpatients annually. Over 80% of UTIs are caused by uropathogenic Escherichia coli (UPEC), and the vast majority of these infections cause bladder infection. Previous data from female patients, who are disproportionately affected, suggest that their disease history may impact the nature of how UPEC interacts with their urinary tract mucosa, altering their susceptibility to future episodes.

"Previous studies in mice have found that susceptibility to recurring UTI (rUTI), resulting from a prior infection, was caused in part by bladder remodeling," says co-lead author Lu Yu, who was a graduate student at Washington University School of Medicine in St Louis, US, at the time the study was conducted. "However, the molecular mechanisms by which this remodeling impacted susceptibility to rUTI were unclear. In this study, we wanted to see why a prior UTI changes the way the urinary bladder responds to subsequent Escherichia coli bacteria. As these bacteria are becoming increasingly resistant to antibiotics, we need to learn more about why UTI may occur again and again in some women but not others."

To do this, the team investigated the nature of acute inflammation during the first 24 hours of UPEC infection in mice that differed only in their disease history. Their work identified distinct patterns of bladder inflammation that dictated the severity of recurrent infections in the animals.

"We found that mice with a history of a self-resolving infection have a robust, early-onset pulse of TNFα signaling that makes them more resistant to severe recurrent infection," explains co-lead author Valerie O'Brien, also a graduate student at Washington University School of Medicine in St Louis at the time the study was done. "On the other hand, those with a history of a long-lasting infection also have robust, early-onset TNFα signaling, but it is sustained throughout the first 24 hours, contributing to bladder mucosal damage that makes them more susceptible to severe recurrent infection."

O'Brien adds that when the TNFα gene in mice with a history of a self-resolving infection is turned on strongly, but for a short amount of time only, there is just enough of an immune response to clear out the bacteria, without damaging the bladder. But it remains to be seen exactly how the TNFα signaling response is dampened so rapidly in these animals.

"Our work so far demonstrates a central role that TNFα plays in the bladder's response to UPEC infection in mice, and shows that the effects of this response can vary substantially depending on the host's history of infection," says co-senior author Thomas Hannan, Instructor in Pathology & Immunology at Washington University School of Medicine in St Louis.

Co-senior author Scott Hultgren, Helen L. Stoever Professor of Molecular Microbiology at the same institute, adds: "Improving our understanding of this underlying host mechanism will be essential for developing new therapies that target the host inflammatory response as an alternative strategy against rapidly increasing antimicrobial resistance."

More information: Lu Yu et al. Mucosal infection rewires TNFα signaling dynamics to skew susceptibility to recurrence, *eLife* (2019).

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