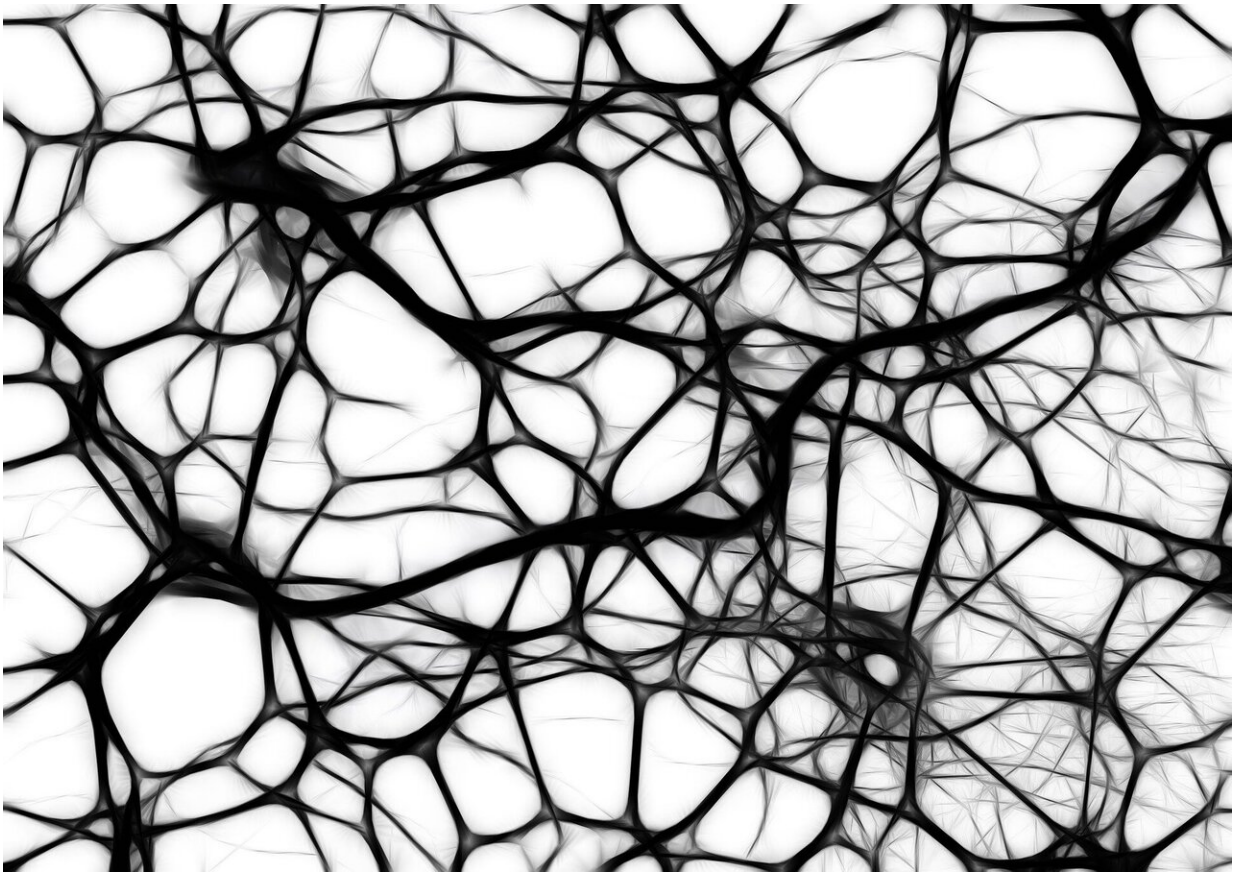
Unusual immune response in bladder appears to drive repeat UTIs

May 19 2020, by Sarah Avery



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As many people know, bladder infections can be a painful and recurring condition, and those who are prone to the infections often report they

have to "go" with greater frequency and urgency.

These two related conditions are caused by an aberrant immune response that prioritizes repairing tissue in the bladder wall over clearing the bacteria, according to a new study led by Duke Health researchers.

The researchers said the findings, publishing online May 18 in the journal *Nature Immunology*, improve the possibility of identifying more effective ways to treat urinary tract infections, or UTIs, which are especially common among women.

"Most women will experience at least one UTI in their lifetime," said senior author Soman Abraham, Ph.D., a professor in the departments of Pathology, Immunology and Molecular Genetics and Microbiology at Duke University School of Medicine. "In a substantial proportion of these women, UTIs become recurrent with painful frequency."

To study the immune response, Abraham and colleagues infected mouse bladders with E.coli. Throughout the body, immune responses to infections are generally balanced between bacterial clearance and tissue repair. However, in the bladder, the response prioritizes tissue repair—a tendency that increases with each successive infection.

Researchers learned that the bladder's initial response emphasizes shedding cells from internal walls to reduce bacterial load. Large numbers of bacteria bind to bladder cell surfaces, so shedding this wall tissue is a natural immune defense. However, the sloughing process removes the thick plaque of cells that protects the bladder walls from salts and toxins in urine. Loss of this barrier exposes the underlying bladder tissue, leading to severe bladder wall damage and pain.

"Because of the harm urine can cause to the unprotected bladder wall, it is not surprising the bladder prioritizes recovery of its plaque-covered

inner wall lining over bacterial clearance during infection," said graduate student Jianxuan Wu, lead author of the study.

The pain caused by urine-induced tissue damage is a greater immediate threat than the bacteria that persist in the bladder, according to the researchers. This focus on bladder wall repair hampers complete clearing of bacteria from the bladder, leaving behind pathogens that bloom into another infection.

With each recurring UTI, the researchers reported, bladder tissue repair occurs more robustly and at a faster rate, resulting in a markedly thicker bladder cell lining. In mice that had experienced multiple UTIs, this physical change reduced bladder capacity and increased voiding frequency. Both symptoms are common among patients who experience recurrent UTIs.

"Our finding that the bladder's predisposition to repeated infections is actually the result of an aberrant immune response could be welcome news because it raises the possibility of therapeutic intervention," Abraham said.

More information: Jianxuan Wu et al. A highly polarized TH2 bladder response to infection promotes epithelial repair at the expense of preventing new infections, *Nature Immunology* (2020). DOI: 10.1038/s41590-020-0688-3

Provided by Duke University