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Host–pathogen biology intertwines in recurrent UTI

Evidence that bacterial infection shapes susceptibility to recurrent UTI via epigenetic memory shows that integrated approaches that consider host and pathogen are essential to develop effective treatments.

One in every two women will likely suffer from a urinary tract infection (UTI) during their lifetime, with at least a third of them suffering subsequent infections within a year. This means that recurrent UTIs affect approximately a sixth of the female population. These painful, debilitating infections, predominantly caused by uropathogenic *Escherichia coli* (UPEC), but also sometimes by ESKAPE pathogens including *Enterococcus* spp., *Staphylococcus* spp. and *Acinetobacter baumannii*, also affect children, older men and those using catheters. If infection is not cured, bacteria can reach the kidneys and disseminate further, sometimes causing sepsis. Despite the burden of disease being so high, with potentially severe or fatal consequences, treatment and prevention options are limited. Antibiotics are typically used, but drug resistance among UPEC is increasing. As antibiotics also disrupt resident microbiotas, and dysbiosis in vaginal and gut microbiotas is linked with UTI susceptibility[1,2], antibiotic use may increase infection risk for UTI.

There is a clear, unmet need for alternative, targeted strategies to treat UTIs. Meeting that need requires a better understanding of UTI pathology, including bacterial virulence and metabolic strategies, effects from local microbiotas and delineation of host immune responses. Identifying crucial bacterial virulence factors has provided some progress. Type I pili, for example, are hair-like surface structures found on UPEC, which use the tip adhesin FimH to bind mannose-containing glycans that coat the host epithelium. Without initial attachment, no intracellular infection can occur. Approaches to disrupt this interaction using mannose-based therapeutics have shown promise, both in mice[3] and in clinical trials involving women with recurrent UTI[4]. A FimH-based vaccine and synthetic galactosides that block a second UPEC pilus involved in kidney adhesion are also under development[5,6]. We now need to see how these approaches reduce and prevent recurrent UTI.

Alongside these anti-virulence strategies, which block pathogen adhesion, other features of the infection process could potentially be targeted by new therapeutics. Expression of core functions, including those related to bacterial metabolism, by human UPEC isolates correlates with effective bladder colonization in mice[7], which argues for more exploration of the metabolic and nutritional strategies contributing to the infectious process. With a sufficient understanding of essential pathogen-specific pathways, strategies targeting metabolic weak points could be designed, or suitable probiotics could be engineered, to counter infection. We must explore, however, whether this could be achieved without collateral damage effects on local microbiota. Another contributing factor in UTI is the nature and extent of inflammation. The ability of UPEC to colonize the bladder correlates with inflammation levels in the human patients from whom strains were isolated[7], while recurrent UTI associates with a low-grade inflammatory signal in the gut microbiota[1]. Inflammation driven by vaginal dysbiosis can also instigate emergence of UPEC from intracellular niches, reinitiating infection[2]. So the question arises, is this host inflammatory response counterproductive and should it be targeted therapeutically?

On UPEC infection, an acute inflammatory response occurs that is associated with cytokines such as IL-6 and TNF, and an influx of monocytes and neutrophils. Programmed cell death responses and exfoliation of infected epithelial cells drive the clearance of bacteria. If this inflammatory response is prolonged or excessive, cell loss and neutrophil recruitment cause tissue damage, disrupt barrier function and expose underlying cells to bacterial invasion. Given that treatment with non-steroidal anti-inflammatory drugs can reduce symptoms and infection levels[8], inflammation is clearly somewhat double edged: while it can be protective, it has the potential to exacerbate disease.

Dual effects of the host response have long-term consequences for host susceptibility to UTI. Experiments in mice are almost bimodal. While some animals mount a regulated, effective inflammatory response that clears UPEC, and that protects against recurrent infection, in others the response is excessive and prolonged. These animals cannot eliminate infection and are left with permanent changes in cell morphology and mucosal immune responses that render them susceptible to recurrent UTIs[9]. In this issue, Russell and colleagues report that susceptibility to recurrent UTIs in mice is linked to epigenetic remodelling of the genome that in turn increases chromatin accessibility and upregulates expression of genes affecting stem cell differentiation, pro-inflammatory responses and cell death pathways. As a result, affected tissues become primed for a maladaptive immune response. If the molecular mechanisms involved can be identified, it may be possible to devise methods to counter UTI 'imprinting' and thereby relieve individuals from the burden of recurrent disease.

Many questions remain, including what drives the heterogeneity in response to initial infection. What are the factors pushing the balance of infection towards resolution in some individuals, and predisposing other, susceptible individuals towards an excessive immune response and maladaptive training of subsequent responses? Does heterogeneity in the infecting bacterial population matter? Do interactions within the various host microbiotas somehow alter bacterial behaviour, or prime immune functions? Are there other underlying host genetic, epigenetic, metabolic or environmental factors that push the inflammatory equilibrium to one side or another?

In order to answer these questions, we will likely need integrated approaches that can be applied to map out the complex interplay between pathogen infection processes and host defences. As we move towards the overarching goal of resolving the burden of recurrent UTI, it is possible that the insights gained, and experimental tools developed,

will translate into generalizable insights into mechanisms of bacterial pathogenesis that will benefit therapeutic development for other, complex, recurrent infections.

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