GENETICS

TLR4 promoter variants influence response to UTI

Catharina Svanborg and colleagues have shown that differential expression of Toll-like receptor 4 (TLR4), driven by variations in the sequence of the gene's promoter, affects the magnitude of the innate immune response of humans to uropathogenic bacteria.

The great range of susceptibility to urinary tract infection (UTI) has traditionally been attributed to differences in voiding efficiency, as well as to social and environmental factors. In the past few years, evidence has accumulated to support a role for genetic variability in differential susceptibility. Research has focused on TLRs, which have a central role in the innate immune response to microbial attack. Failure to identify polymorphisms that affect the structure of TLRs led investigators to turn their attention to expression of these receptors.

Svanborg *et al.* showed previously that mice in which expression of Tlr4 is deficient are highly susceptible to UTI. Clearance of bacteria is slow in these animals, but they remain asymptomatic and are not prone to sepsis or renal damage. The team, which includes members from Sweden and Singapore, wanted to determine if TLR4 expression has a similar role in humans.

"The results from the mouse model predicted that low TLR4 expression would protect against a full innate immune response and thus be found in patients with asymptomatic bacteriuria rather than [in those with] severe, symptomatic infections" explains Svanborg. It was important, therefore, to clearly define three distinct study groups; patients with asymptomatic bacteriuria, those prone to recurrent acute pyelonephritis, and controls from the general population.

The researchers assembled small cohorts of both children (51 cases) and adults. The 62 adults had a childhood history of pyelonephritis and had participated in a study of febrile UTI in the 1970s.

Sequencing of the *TLR4* promoter of age-matched controls revealed a total of eight single nucleotide polymorphisms (SNPs). Individuals harbored different combinations of these SNPs, resulting in almost 30 different genotype patterns in the general Swedish population. Fewer of these patterns were detected in the group of patients with asymptomatic infections. The promoter sequence variants that were present in the asymptomatic group ameliorated expression of TLR4 in response to experimental infection.

All eight SNPs were detected in the group of patients with pyelonephritis, and the number of genotype patterns did not differ markedly from that in the control cohort. These findings support the authors' hypothesis that reduced TLR4 expression dampens the innate mucosal response to uropathogenic bacteria, promoting an asymptomatic carrier state and protecting against severe disease.

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Original article Ragnarsdóttir, B. *et al.* Toll-like receptor 4 promoter polymorphisms: common TLR4 variants may protect against severe urinary tract infection. *PLoS ONE* 5, e10734 (2010)