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INFECTION

Blocking bacterial biofilms on urinary bladder catheters

New research has identified an interaction between a bacterial protein and fibrinogen that is found in the murine bladder following catheterization, enabling formation of a bacterial biofilm on the catheter, which is prevented by vaccination of mice with the bacterial protein.

Catheter-associated urinary tract infections (CAUTIs) are the most common cause of hospital-acquired infections. The emergence of drug-resistant bacteria has reduced available treatment options for CAUTIs, and new therapeutic strategies are urgently required.

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Enterococci account for 15% of CAUTIs, and the pathogenesis of *Enterococcus faecalis* UTI derives from its ability to form biofilms on catheters—*E. faecalis* is highly attenuated in the absence of catheterization in a murine model. A bacterial pilus consisting of three protein subunits contributes to biofilm formation; the EbpA subunit, which forms the tip of the pilus, is known to be involved in CAUTI.

The N-terminal domain of EbpA contains a MIDAS motif, which is typically involved in cellular adherence. Deletion or mutation of the EbpA MIDAS motif diminished *in vitro* biofilm formation. Sequence analysis of the EbpA N-terminus suggested the presence of a fibrinogen-binding domain. *In vitro*, fibrinogen binding was observed with wild-type EbpA, but not with the mutant isoforms.

In a murine model of urinary bladder catheterization, fibrinogen was found to be released into the bladder as early as 1 h after catheter implantation. When catheterized mice were challenged with wild-type *E. faecalis*, the bacteria colocalized with fibrinogen on the catheter and on bladder urothelium, whereas *E. faecalis* lacking wild-type EbpA were not detected on either surface.

The requirement for fibrinogen in *E. faecalis* biofilm formation was further demonstrated by the observation of poor bacterial growth in human urine *in vitro*. Supplementation of the urine with fibrinogen stimulated biofilm formation by wild-type bacteria, but not by bacteria with EbpA MIDAS-motif mutations. Furthermore, vaccination of mice with either full-length EbpA protein or the EbpA N-terminal domain produced a long-lasting immune response that protected the animals against CAUTI induced by *E. faecalis*. Sera from vaccinated mice blocked the interaction between EbpA and fibrinogen *in vitro*.

Vaccinations targeting bacterial biofilm formation could provide a new therapeutic approach for prevention of CAUTIs. Whether this model is transferable to humans and to other CAUTI pathogens must now be tested.

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Original article Flores-Mireles, A. L. *et al*. EbpA vaccine antibodies block binding of *Enterococcus faecalis* to fibrinogen to prevent catheter-associated bladder infection in mice. *Sci. Transl. Med.* **6**, 254ra127 (2014)