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Mouse model of Gram-negative prosthetic joint infection reveals therapeutic targets

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Abstract

Bacterial biofilm infections of implantable medical devices decrease the effectiveness of antibiotics, creating difficult-to-treat chronic infections. Prosthetic joint infections (PJI) are particularly problematic because they require prolonged antibiotic courses and reoperations to remove and replace the infected prostheses. Current models to study PJI focus on Gram-positive bacteria, but Gram-negative PJI (GN-PJI) are increasingly common and are often more difficult to treat, with worse clinical outcomes. Herein, we sought to develop a mouse model of GN-PJI to investigate the pathogenesis of these infections and identify potential therapeutic targets. An orthopedic-grade titanium implant was surgically placed in the femurs of mice, followed by infection of the knee joint with Pseudomonas aeruginosa or Escherichia coli. We found that in vitro biofilm-producing activity was associated with the development of an in vivo orthopedic implant infection characterized by bacterial infection of the bone/joint tissue, biofilm formation on the implants, reactive bone changes, and inflammatory immune cell infiltrates. In addition, a bispecific antibody targeting P. aeruginosa virulence factors (PcrV and Psl exopolysaccharide) reduced the bacterial burden in vivo. Taken together, our findings provide a preclinical model of GN-PJI and suggest the therapeutic potential of targeting biofilm-associated antigens.

Keywords: Bacterial infections; Infectious disease; Mouse models; Therapeutics.