Protective role of IL-1β against post-arthroplasty Staphylococcus aureus infection

INTRODUCTION:

As the number of total joint arthroplasty surgeries in the United States will exceed 3.8 million surgeries per year by 2030, the number of post-arthroplasty infections is projected to increase to over 266,000 infections annually. The treatment of these infections will exhaust healthcare resources and dramatically increase medical costs. In our previous work, we developed a mouse model of post-arthroplasty Staphylococcus aureus infection using in vivo bioluminescence imaging to monitor bacterial burden in real-time and assess the efficacy of an antimicrobial polymer coating in the prevention of the infection. In the present study, we utilized this model to evaluate immune responses that may potentially provide protection against these infections. Specifically, we evaluate the role of IL-1β and TNFα, pro-inflammatory cytokines, as well as Toll-like receptor 2 (TLR2), a pattern recognition receptor that recognizes S. aureus lipopeptides and lipoteichoic acid.

METHODS:

All procedures were approved by the UCLA Animal Research Committee (ARC#: 2008-112). 12-week old male mice on a C57BL/6 background were used in all experiments. To simulate a post-arthroplasty infection, the distal right femur was accessed through a medial parapatellar arthrotomy with lateral displacement of the quadriceps-bicep. An orthopaedic-grade stainless steel Kirschner (K)-wire (diameter 0.6 mm) (Synthes) was placed in a retrograde fashion into the femur and cut with 1 mm protruding into the joint space. The Xen36 S. aureus strain [Caliper Life Sciences] (1e3 CFUs) in a 2 µl volume was inoculated into the joint space of IL-1β deficient, TLR2-deficient, TNFα-deficient and wildtype mice. Bacterial burden within the infected post-operative knee joints was measured with in vivo bioluminescence imaging on post-operative days 0, 1, 3, 5, 7, 10 and 14. Statistical differences between knockout mice and wildtype mice were determined by a Student’s t test (two-tailed). Biofilm formation on the intra-articular portion of the implant was assessed using variable pressure scanning electron microscopy (VP-SEM).

RESULTS:

IL-1β-deficient mice had significantly increased bacterial burden compared with wildtype mice

IL-1β-deficient mice had up to 56-fold greater bacterial burden as measured by in vivo bioluminescence compared with wildtype mice (Figure 1A). The greatest increase in bacterial burden in IL-1β-deficient mice was seen on day 1, but was also statistically greater than the signals of wildtype mice on post-operative days 3 and 5.

TLR2-deficient mice had similar bacterial burden as wildtype mice

TLR2-deficient mice had in vivo bioluminescence signals that did not significantly differ from those of wildtype mice as measured by in vivo bioluminescence (Figure 1A).

TNFα-deficient mice had similar bacterial burden as wildtype mice.

TNFα-deficient mice had in vivo bioluminescence signals that did not significantly differ from the signals of wildtype mice as measured by in vivo bioluminescence (Figure 1B).

Biofilm formation was qualitatively more pronounced in IL-1β-deficient mice imaged on variable pressure scanning electron microscope (VP-SEM).

Implants from IL-1β-deficient mice and wildtype mice were harvested after the experiment and biofilms were assessed by using VP-SEM. Both IL-1β-deficient mice and wildtype mice developed biofilms on the implant surface. However, there appeared to be more prominent biofilm formation on the implants from IL-1β-deficient mice (Figure 2).

DISCUSSION:

Using our previously developed mouse model of post-arthroplasty S. aureus joint infection, we were able to study the roles of proinflammatory mediators in the early immune response. We found that IL-1β-deficient mice had a markedly increased bacterial burden compared to wildtype mice, which was most pronounced at post-operative day 1. Interestingly, TLR2-deficient mice did not show increased bacterial burden despite the fact that TLR2 promotes immune responses through the same MyD88-signaling pathway as IL-1β. TNFα-deficient mice also did not show an increased bacterial burden compared to wildtype mice. Although biofilm formation was present on implants from wildtype and IL-1β-deficient mice, the biofilms were qualitatively more prominent on implants harvested from IL-1β-deficient mice. Taken together, these findings demonstrate an important role for IL-1β in the early control of bacterial burden in a post-surgical joint. Further investigation is required to determine whether immune modulation of the IL-1β protective immune response may provide a novel strategy to help prevent post-arthroplasty infections.