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CXCR2 perturbation promotes *Staphylococcus aureus* implant-associated infection

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Abstract

Introduction. *Staphylococcus aureus* is the leading cause of acute medical implant infections, representing a significant modern medical concern. The success of *S. aureus* as a pathogen in these cases resides in its arsenal of virulence factors, resistance to multiple antimicrobials, mechanisms of immune modulation, and ability to rapidly form biofilms associated with implant surfaces. *S. aureus* device-associated, biofilm-mediated infections are often persistent and notoriously difficult to treat, skewing innate immune responses to promote chronic reoccurring infections. While relatively little is known of the role neutrophils play in response to acute *S. aureus* biofilm infections, these effector cells must be efficiently recruited to sites of infection via directed chemotaxis. Here we investigate the effects of modulating CXC chemokine receptor 2 (CXCR2) activity, predominantly expressed on neutrophils, during *S. aureus* implant-associated infection.

Hypothesis. We hypothesize that modulation of CXCR2 expression and/or signalling activities during *S. aureus* infection, and thus neutrophil recruitment, extravasation and antimicrobial activity, will affect infection control and bacterial burdens in a mouse model of implant-associated infection.

Aim. This investigation aims to elucidate the impact of altered CXCR2 activity during *S. aureus* biofilm-mediated infection that may help develop a framework for an effective novel strategy to prevent morbidity and mortality associated with implant infections.

Methodology. To examine the role of CXCR2 during *S. aureus* implant infection, we employed a mouse model of indwelling subcutaneous catheter infection using a community-associated methicillin-resistant *S. aureus* (MRSA) strain. To assess the role of CXCR2 induction or inhibition during infection, treatment groups received daily intraperitoneal doses of either Lipocalin-2 (Lcn2) or AZD5069, respectively. At the end of the study, catheters and surrounding soft tissues were analysed for bacterial burdens and dissemination, and *Cxcr2* transcription within the implant-associated tissues was quantified.

Results. Mice treated with Lcn2 developed higher bacterial burdens within the soft tissue surrounding the implant site, which was associated with increased *Cxcr2* expression. AZD5069 treatment also resulted in increased implant- and tissues-associated bacterial titres, as well as enhanced *Cxcr2* expression.

Conclusion. Our results demonstrate that CXCR2 plays an essential role in regulating the severity of *S. aureus* implant-associated infections. Interestingly, however, perturbation of CXCR2 expression or signalling both resulted in enhanced *Cxcr2* transcription and elevated implant-associated bacterial burdens. Thus, CXCR2 appears finely tuned to efficiently recruit effector cells and mediate control of *S. aureus* biofilm-mediated infection.

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Abbreviations: CXCR2, CXC chemokine receptor 2; H&E, hematoxylin and eosin; IL-10, interleukin 10; Lcn2, lipocalin-2; S. aureus, Staphylococcus aureus.