Staphylococcus aureus Biofilms Actively Promote Innate Immune Dysfunction

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Staphylococcus aureus (S. aureus) is a leading cause of infections involving indwelling medical devices, including prosthetic joints, where bacteria have the propensity to form biofilms. Biofilm infections are extremely difficult to eradicate based on their recalcitrance to antibiotics, and typically require removal of the contaminated device, whereupon a new implant is inserted. Our laboratory has established a critical role for myeloid-derived suppressor cells (MDSCs) in promoting S. aureus biofilm persistence, in part, through IL-10 production, which skews biofilm-associated monocytes toward an anti-inflammatory state. Based on the critical role of IL-10 in regulating MDSC-monocyte crosstalk during biofilm infection, we designed a screen of the Nebraska Transposon Mutant Library to identify S. aureus mutants impaired in their ability to trigger IL-10 production. Significant hits involved in lactate biosynthesis were identified, suggesting that lactate is an important regulator of MDSC and monocyte activation. This talk will describe evidence supporting an active role for S. aureus-derived lactate in organizing the anti-inflammatory biofilm milieu, progressing from MDSCs/monocytes as a target to defining the molecular mechanism of action. Using a mouse model of orthopedic implant biofilm infection, D- and L-lactate levels were reduced with S. aureus ddh1 and ldh1/ldh2 mutants, respectively, which coincided with significant reductions in MDSC infiltrates and IL-10 production and translated into enhanced monocyte and neutrophil recruitment and improved biofilm clearance. The IL-10 promoter is activated by acetylation and ChIP-Seq data have demonstrated that histone H3K9 promoter acetylation was dramatically increased genome-wide in leukocytes recovered from wild type vs. S. aureus lactate mutant infected mice, providing molecular evidence that S. aureus biofilm-derived lactate functions as a histone deacetylase inhibitor (HDACi) to augment transcriptional activation of the IL-10 promoter and attenuate leukocyte antibacterial activity. Supported by NIAID 2P01AI083211 (Project 4 to T.K.)