Transcriptomic Characterization of Acute Implant Associated Infection

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INTRODUCTION: Implant-Associated Infections (IAI), primarily caused by Staphylococcus aureus (*S. aureus*), are significant complications in orthopedic surgery, and lead to prosthetic failure. Diagnosis, and determining severity and antimicrobial sensitivity are hindered by bacterial persistence. The gene expression and immune response networks in IAI, especially the difference between methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) associated infections, remain incompletely understood.

METHODS: We established a subcutaneous IAI model using methicillin-sensitive MSSA and MRSA and analyzed implant capsule tissues across multiple time points (POD0, 1, 3, 7) using RNA bulk sequencing. Analyses of differential expressed gens (DEGs), ssGSEA, CIBERSORTx, KEGG and GO enrichment, MFUZZ, ESTIMATE, PPI/hub genes, correlation and ROC/AUC were employed to identify diagnostic markers and characterize immune cell infiltration profiles. Additionally, comparative immune profiling was conducted on a public clinical (PJI) dataset and other preclinical (mice PJI) datasets.

RESULTS SECTION: Transcriptomic analysis identified DEGs associated with *S. aureus* (MSSA/MRSA). The top upregulated genes with infection were immune-related genes such as Cxcl6, Cxcl3 and Saa3 (Fig 1). Cytokine-cytokine receptor interactions and chemokine signaling pathways were prominent acutely. MRSA infections exhibited decreased expression of Il17a, and Cd300c. Immune infiltration analysis showed an increase in natural killer (NK) cells, monocytes, and T-helper 1 (Th1) cells in MSSA infections, with Th17 cells significantly reduced in MRSA (Fig 2). The predicted proportion of NK and NK T cell were positively correlated with Il17a and Cxcl6. Our analysis regarding Th1 and Th17 cells in the rat model was consistent with that in a MRSA-infected murine PJI model (GSE 242039), the trends of NK cells were consistent with that in sonicate fluid sample from PJI patients (GSE 255786).

DISCUSSION: Our study elucidates the transcriptional characterization in a MSSA/MRSA IAI model, identifying key diagnostic markers and immune networks. These findings provide a basis for estimating infection severity in preclinical models across species, modulating NK and T cell mediated immunity, and guiding implant modifications for improved clinical outcomes.

SIGNIFICANCE/CLINICAL RELEVANCE: The sustained elevation of Cxcl6, Cxcl3, and Saa3 across time points suggests their potential as diagnostic biomarkers for acute. This signature, combined with decreased expression of Il17a, Cd300c and impaired Th17 cells influx could may represent a characteristic trend specific to acute MRSA IAI.

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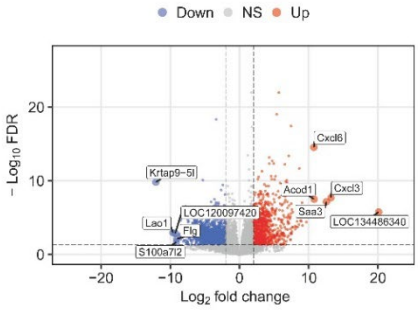

Fig. 1 Volcano plot for DEGs analysis comparing *S. aureus* IAI group to NC.

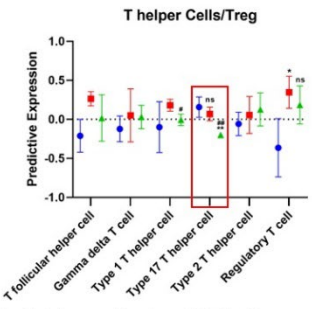

Fig. 2 Predicted proportion by ssGSEA of immune cells (compared to, NC (**p < 0.01) , MSSA (##p < 0.01)).

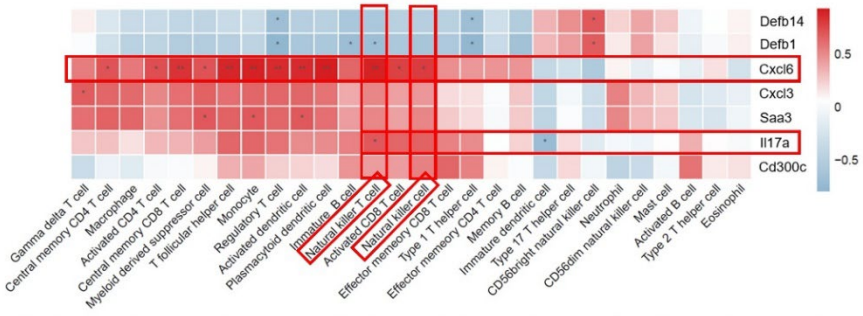

Fig. 3 Heatmap was presented to show the Spearman's correlation result on the differential expressed gene on top upregulated/downregulated and different immune (*p < 0.05, **p < 0.01).