Metabolic Reprogramming of Synovial Macrophages as a Therapeutic Target in MRSA Septic Arthritis

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INTRODUCTION: Bacterial joint infections pose a significant clinical challenge because Staphylococcus aureus can invade host cells and persist despite antibiotic treatment. Unlike soft tissue infections, septic arthritis rapidly damages cartilage, which cannot regenerate once destroyed. We hypothesized that MRSA (methicillin-resistant Staphylococcus aureus) drives a transcriptional and metabolic reprogramming of synovial macrophages that sustains inflammation and joint damage, and that targeting metabolic reprogramming may provide a therapeutic strategy.

METHODS: We developed a murine model of MRSA-induced septic arthritis by intra-articular injection of the knee joint (n=24, 6 male and 6 female C57BL/6J mice each group, 12 weeks old). Control (Con) and MRSA-infected (MRSA) joints were profiled using 10x Genomics Visium spatial transcriptomics. Cell populations were annotated, and regulon-based transcription factor (TF) activity was assessed. Gene set variation analysis (GSVA) was performed to evaluate metabolic pathway enrichment, and Pearson correlations were calculated between TF activity and inflammatory gene expression. In vivo and in vitro macrophage infection experiments validated transcriptomic findings. Dimethyl fumarate (DMF), a glycolysis-targeting drug, and vancomycin were tested alone or in combination for therapeutic efficacy. All animal studies were approved by the Yale University Institutional Animal Care and Use Committee.

RESULTS SECTION: Spatial profiling revealed a robust expansion of pro-inflammatory synovial macrophages and MHCII$^+$ infiltrating macrophages in MRSA-infected knees, localized within Col1a1$^+$ stromal compartments. Regulon analysis identified Fos as a top-ranked TF, with activity strongly and positively correlated with Il1b, Mmp3, Mmp9, Nos2, Ccl5, and Nfkb1. GSVA showed a significant upregulation of glycolysis in infiltrating macrophages ($p<0.05$), which was confirmed by functional assays demonstrating increased glycolytic flux after MRSA infection. DMF treatment reduced macrophage glycolysis, suppressed MAPK pathway activity, decreased Fos expression, and attenuated inflammatory cytokine release. Combined DMF and vancomycin therapy synergistically reduced bacterial load and recurrence, alleviated joint swelling, and preserved cartilage and bone structure.

DISCUSSION: MRSA infection reprograms synovial macrophages into a Fos-driven pro-inflammatory state characterized by heightened glycolysis, thereby sustaining joint inflammation and tissue damage despite antibiotic therapy. Targeting macrophage metabolism with DMF both limited bacterial survival and reduced destructive inflammation. Limitations include reliance on a murine model and the need for validation in human septic arthritis.

SIGNIFICANCE/CLINICAL RELEVANCE: This study identifies macrophage glycolysis as a key driver of MRSA septic arthritis and highlights DMF as a promising adjunct to antibiotics. By reducing bacterial burden and protecting cartilage, metabolic reprogramming strategies may address a critical unmet need in musculoskeletal infection management.