Proteomic Insight into Immune Pathways and Biomarker Discovery in Periprosthetic Joint Infection

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INTRODUCTION:

Periprosthetic joint infection (PJI) is a severe complication of joint arthroplasty with poorly understood immune mechanisms. This study aimed to identify immune proteins and pathways activated or suppressed during infection.

METHODS:

Synovial fluid samples were prospectively collected from three patient groups during arthroplasty surgeries between August 2023 and September 2024: primary total knee arthroplasty (TKA, n=9), aseptic revision (n=10), and septic revision (n=14, per 2018 ICM criteria). Proteomic analysis using the 1500 SomaScan assay was calculated for fold-change (Aseptic or Septic/TKA) with log2 transformation. Statistical analysis included Wilcoxon rank-sum and Kruskal-Wallis tests, with significant proteins defined by ≥2-fold change and $p \le 0.05$.

RESULTS:

Compared to TKA, septic revisions revealed 20 upregulated and 126 downregulated proteins, while aseptic revisions showed five upregulated and six downregulated proteins. Eight proteins were commonly regulated in both aseptic and septic groups, suggesting arthroplasty-related expression. Key immune pathways showed significant upregulation in septic samples, including immune response proteins—VVN2 (12.5, $p < 0.001$), C3 (2.09, $p < 0.05$), HLA-DOB (4.37, $p < 0.001$)—and antimicrobial proteins—DEFA4 (5.96, $p < 0.01$), LCN2 (47.03, $p < 0.001$), LTF (2.02, $p < 0.01$). Conversely, marked downregulation was observed in immune modulation proteins—LAG3 (-3.91, $p < 0.001$), CD28 (-6.97, $p < 0.001$), IL-17RA (-10.64, $p < 0.001$)—and signaling proteins—STAT1 (-5.29, $p < 0.001$), PRKCA (-4.34, $p < 0.001$).

DISCUSSION AND CONCLUSION:

This first comprehensive proteomic analysis of synovial fluid in PJI reveals distinct protein expression and pathway activation, advancing understanding of infection pathophysiology and identifying potential biomarkers. These findings highlight previously underexplored immune responses in PJI and may inform future studies aimed at diagnostic biomarker discovery and a deeper understanding of the pathophysiology of joint infection.

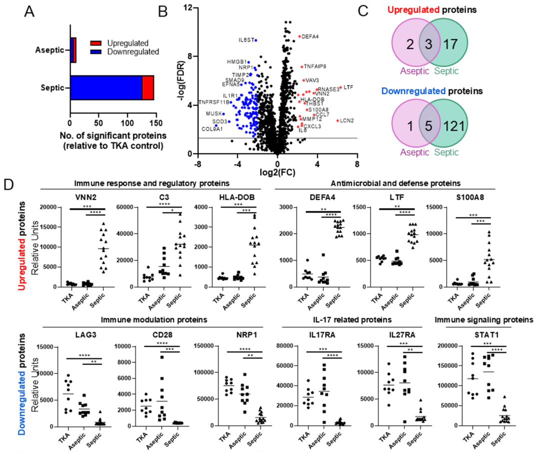

Figure 1. Differential protein expression between TKA, aseptic revision, and septic revision. (A) Number of upregulated and downregulated proteins compared to TKA control **(B)** Volcano plot of TKA vs. septic revision. Significantly downregulated (blue) and upregulated (red) proteins ≥4-fold are highlighted in the plot. **(C)** Venn diagram of significantly regulated proteins that are shared between revision groups. **(D)** Significantly upregulated and downregulated proteins in septic group related to immune pathways.