Immunologic Markers of Dormant Infection Predict Infection Free Survival in Total Joint Replacements

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INTRODUCTION:

The ability of biofilm-resident bacteria to regulate the immune response coupled with the overreliance current diagnostic criteria for infected joint replacements on the local and systemic neutrophil response means that biofilm-resident bacteria may establish a dormant infection that is misclassified as uninfected. We hypothesize that joint replacements with a prior infection have a high prevalence of dormant infections that can be distinguished from uninfected joint replacements by the inflammatory response in synovial fluid and/or circulating plasma and that detecting a dormant infection increases the risk of infection recurrence.

METHODS: Proteomic profiling (Olink Proteomics, Sweden) was performed on matched whole blood and synovial fluid samples collected 7 joint replacements had an active infection, 12 joint replacements without an infection, and 11 joint replacements with a prior infection deemed “infection-free” after spacer placement by the 2018 Musculoskeletal Infection Society criteria. We used differential expression, hierarchical clustering, principal component, and gene set variation analyses to characterize dormant infections and correlated them to the incidence of infection recurrence at a mean follow-up of 3.0 ± 0.2 years.

RESULTS: Hierarchical cluster analysis of synovial inflammatory proteomics categorized 8 of the joint replacements with a prior infection (72%) as infected in the absence of systemic acute phase reactants with a lack of synovial neutrophil recruitment defining them as dormant infections. CXCL5 expression, which was expressed in both active and prior infection distinguished these synovial samples from the uninfected joint replacements. PDGF subunit B, Gal-1, CXCL11, ANGPT1, EGF, TIE2, MCP-2, and NOS3 had an accuracy and importance that exceeded that of CXCL5 (AUC=0.897, %IncMSE=1.7). Plasma inflammatory proteomics comparing the dormant infections to uninfected joint replacements revealed no statistical differences. Dormant infections displayed downregulation of inflammatory pathways involved in granulocyte activation as well as T-cell selection and proliferation when compared to uninfected joint replacements (FDR<0.001). Two dormant infections had an infection recurrence (22%) at a mean follow-up of 3.0 ± 0.2 years. The biomarkers of dormant infection had a high sensitivity (100%) and negative predictive value (100%) but lacked specificity (61%) and positive predictive value (39%) with modest accuracy (64%) for recurrent infection.

DISCUSSION AND CONCLUSION:

The inability to effectively diagnose a dormant infection has relegated most clinical work on infection to the diagnosis of only the most advanced disease state - systemic sepsis and chronic infection. While it is unclear which the candidate biomarkers present in joint replacements with dormant infection predict infection recurrence, there are three paradigm shifting conclusions from our work. First, the absence of these candidate biomarkers from synovial fluid was an excellent predictor of infection free survival at 3 years with 100% sensitivity and negative predictive value. To our knowledge, this is the first demonstration of a prognostic markers related to the short or mid-term survival of infected joint replacements. Second, the use of systemic acute phase reactants, like ESR and CRP, as screening tests to rule out infection are inadequate. Since the absence of systemic acute phase reactants, does not coincide with the lack of an infection but rather the lack of an infection or the presence of a dormant infection that suppresses the expression of those acute phase reactants. Third, expression of our novel biomarkers provides a culture-free method to monitoring for infection prior to surgery or after antimicrobial therapy.

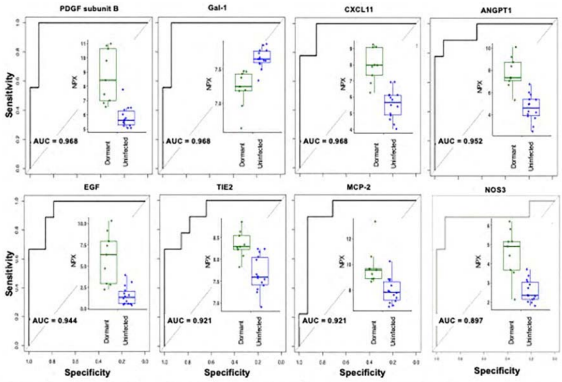

Figure: Candidate Biomarkers that Distinguish Dormant Infections from Uninfected Joint Replacements. Accuracy as measured by area under the curve (AUC) for all candidate biomarkers with a better accuracy than CXCL5, as identified by Euclidean distance-based clustering, for identifying a dormant infection. Embedded box and whisker plots showing the expression of each candidate biomarkers in normalized protein expression (NPX, $\log_2$) for patients with a dormant infection (green) and without an infection (blue).