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S100A9-INDUCED REPROGRAMMING OF MYELOID CELLS DURING SEPSIS

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Introduction/Hypothesis: The premise of this study is derived from published data showing that the initial/acute immune defense response to sepsis rapidly progresses to innate and adaptive immune suppression. We have previously shown that sepsis enhances myelopoiesis and generates immature Gr1+CD11b+ myeloid-derived suppressor cells (MDSCs). MDSCs along with organ- specific immune tolerant cells promote chronic infection and organ dysfunction, and increase sepsis mortality. No molecular based treatments of sepsis exist. The aim of this study was to determine how S100A9 expression alters immune cell function during sepsis.

Methods: We used C57BL/6 mouse and cecal ligation and puncture model of chronic polymicrobial sepsis with immunosuppression, which mimics human peritonitis-induced sepsis, and followed mice for 28 days. Proteins were assessed by ELISA and western blot, and long noncoding RNA was measured by real-time PCR. Exosomes were purified from Gr1+CD11b+ MDSC cultures using filtration spin-columns.

Results: S100A9 protein translocated from cytosol to nucleus in Gr1+CD11b+ MDSCs during late/chronic, but not acute/early sepsis, which led to a decrease in S100A9 protein secretion. Exosomes shed from cultured MDSCs isolated from late septic mice inhibited the LPS-induced secretion of S100A9 from naive Gr1+CD11b+ cells. Long noncoding RNA (lncRNA) expression profiling revealed increased levels of lncRNA Hotairm1 expression in exosomes during late sepsis. The Hotairm1-containing exosomes derived from late sepsis MDSCs, but not MDSCs lacking Hotairm1, suppressed T cell proliferation and activation. Hotairm1 co-immunoprecipitated with S100A9 protein in MDSCs during late sepsis, and Hotairm1 knockdown relocalized S100A9 in cytosol.

Conclusions: Hotairm1 controls S100A9 transport to the nucleus of Gr1+CD11b+ cells during late sepsis to promote immunosuppression. We speculate that nuclear transported S100A9 may directly control repressor gene expression in Gr1+CD11b+ cells, and inform a new molecular target for treating sepsis immunosuppression.

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EFFECTS OF MONOCYTE DISTRIBUTION WIDTH AND WHITE BLOOD CELL COUNT ON A SEPSIS PREDICTION ALGORITHM

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Introduction/Hypothesis: Severe sepsis and septic shock are among the leading causes of death in the US, and early prediction can reduce adverse patient outcomes. We have previously demonstrated that a machine-learning based algorithm (MLA) can accurately predict sepsis using only patient age and vital sign data. In a recent pivotal clinical trial, elevated monocyte-distribution width (MDW) values were observed at 12 and 72 hours prior to development of clinical signs of sepsis (Sepsis-3). This study tests the hypothesis that including MDW and white blood cell count (WBC) data inputs will improve performance of an MLA for sepsis prediction.

Methods: Four gradient boosted tree models (vital signs only, vitals + MDW, vitals + WBC, vitals + MDW + WBC) were trained on data from four hospitals. Vital signs were collected from electronic health records and included diastolic and systolic blood pressure, heart rate, temperature, and respiratory rate. WBC and MDW data were collected using a Beckman Coulter DxH800 system. Sepsis was defined as meeting two SIRS criteria with microbial testing as defined in Rhee 2017. Vital sign only and vital sign + WBC models resulted in inclusion of 9918 patients, 10.2% of whom met sepsis criteria. MDW data resulted in the inclusion of 121 patients due to limited data availability, 14.0% of whom met criteria. Models were trained using 10-fold and leave one out cross-validation and evaluated on a holdout test set.

Results: While Negative Predictive Value (NPV) performance held nearly constant near 0.9, Positive Predictive Value (PPV) increased from 0.75 for vitals only, to 0.86 for vitals + WBC, 0.92 for vitals + MDW, and 0.96 with the inclusion of vitals, MDW, and WBC. For comparison, the MEWS PPV was 0.46 and SOFA was 0.19, both with NPV near 0.9. Across all feature sets, models produced an AUROC>0.95. Specificity increased with WBC and MDW data inclusions.

Conclusions: Results indicate that an MLA trained on vital signs together with WBC and MDW laboratory results can produce improved performance over current sepsis prediction methods. An adaptable MLA with the flexibility to evaluate the inclusion of new sepsis biomarkers has the potential for far-reaching impacts on sepsis treatment and patient outcomes. These results require further validation in an independent prospective study.

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