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Mitogen-activated protein kinase in S. epidermidis CSF shunt infection

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Background: Thousands of CSF shunts are placed each year to treat hydrocephalus, however, this is often complicated by infection. Tragically, these infections are associated with significant long-term neurologic morbidity. The cellular mechanisms underlying this neurologic morbidity are poorly understood. Using single nucleus nuclear RNA sequencing (snRNAseq) we identified acute and chronic transcriptome changes that occur in the brain following CSF shunt infection, providing potential insight into causes of neurologic morbidity.

Methods: Silicone catheters were precoated with S. epidermidis and implanted into the lateral ventricle of the brain in C57BL/6 mice. At days 56 post-infection brain tissue immediately surrounding the catheter was removed and snap frozen for storage and nuclei isolation. SnRNAseq libraries were generated using the 10x Genomics Chromium Controller and sequenced on a NovaSeq 6000. The R package Seurat was used for quality control and to cluster nuclei based on transcriptomic data. Cluster identities were determined by expression of canonical cell-specific genes. Pseudobulk analysis was performed in the R package Libra, allowing identification of differentially expressed genes. Ingenuity Pathway Analysis was used for analysis of canonical pathways and upstream regulators. Mitogen-activated protein kinase (MAPK) abundance was determined via multiplex analysis.

Results: At day 56 post-infection, the majority of DEGs were identified in two neuronal clusters. Interestingly, the largest neuronal cluster and the microglial cluster demonstrated an upregulation of genes in the MAPK pathway which has been implicated in neuroinflammation. Studies are ongoing in the laboratory to determine the quantity of phosphorylated and total proteins in the MAPK pathway.

Discussion: These data indicate that S. epidermidis CSF shunt infection results in long-term transcriptomic changes that differ by cell population. The identification of DEGs, specifically those within the MAPK pathway which has implications in neuroinflammation as well as cell proliferation, differentiation and death requires further investigation to determine this pathway's significance during S. epidermidis shunt infection.