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O0671 Upregulation of host responses to IL-17 and Type 1 interferons in the CSF compartment is associated with poor outcome in adult pneumococcal meningitis

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Background: In populations with high HIV prevalence, causes of high mortality in pneumococcal meningitis (PM) are poorly understood, adjunctive interventions are ineffective or harmful. We previously reported associations between low cerebrospinal fluid (CSF) white cell counts and poor outcome from PM in Malawi. In this study we tested the hypothesis that CSF neutrophil activity was attenuated in non-survivors of PM using transcriptional profiling.

Materials/methods: Pre-antibiotic CSF from adults with proven PM underwent transcriptional profiling with RNA sequencing. Data were mapped with Salmon and analysed using DESeq2 in R. Published functional transcriptional modules were applied to CSF data, module scores were compared by outcome. Pathway analysis on differentially expressed genes between survivors and non-survivors was performed using InnateDB (www.innatedb.com). Network graphs of differentially expressed genes were generated using Ingenuity pathways analysis® (IPA) (Qiagen), XGR and Gephi.

Results: 13 adults with proven pneumococcal meningitis were included. 11/13 were HIV co-infected, the median age was 32 years, and mortality 60%. All patients received parenteral ceftriaxone within 3 hours. No differences in CSF white cell sub-type module expression were observed between outcome groups (Figure 1). In contrast, significantly increased expression of IL-17, IL-10 and Type 1 interferon response module genes in CSF were observed in non-survivors. No differences in module expression for TNF-alpha, Type 2 interferons or IL-4/13 were observed. Differentially expressed genes were co-correlated in a network of pro-inflammatory genes downstream from IL-17, TNF alpha, IL-6 and Interferon alpha in non-survivors, pathways were enriched for collagen degradation, VEGF production, complement activity and platelet degranulation. In contrast, differentially expressed genes in survivor CSF were co-correlated in a network dominated by transcriptional regulation and macrophage apoptosis.

Conclusions: The CSF transcriptome in non-survivors was characterized by marked expression of pro-inflammatory module genes and vaso-active mediators, with no corresponding upregulation in the neutrophil response. Blunting of the neutrophil response in the cerebrospinal compartment in pneumococcal meningitis may partially explain the failure of adjunctive treatments to effect outcome. Future studies will be targeted on understanding the inflammatory disconnect between pro-inflammatory mediators and neutrophil response in PM to identify novel therapeutic targets.

Comparison of transcriptional module expression with clinical outcome in the CSF of adults with proven pneumococcal meningitis

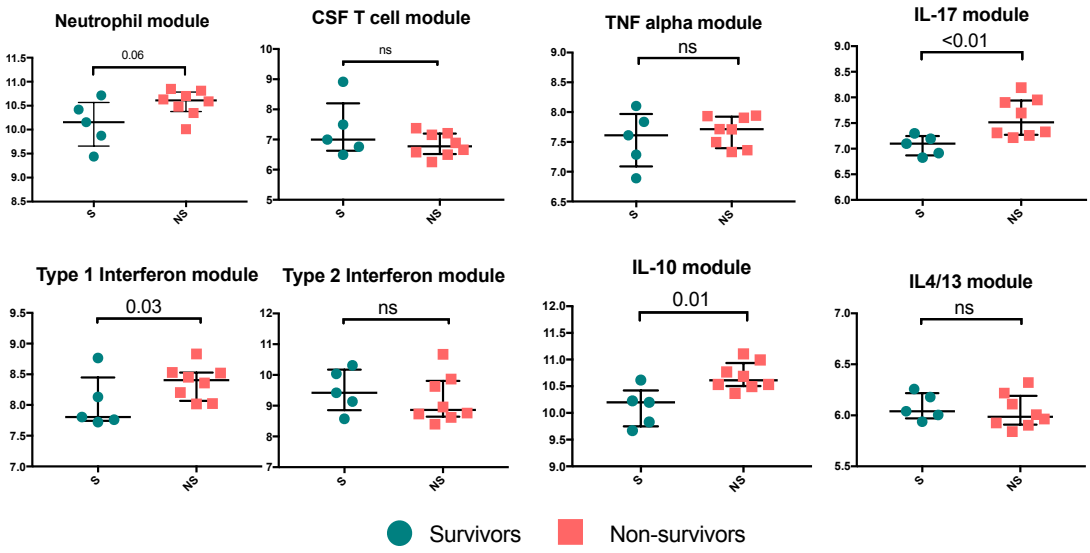

Figure 1: Individual module scores per patient calculated by geometric mean of log $_2$ transformed gene transcript counts per million (CPM) reads across all genes in each module. Bars represent median and interquartile range. Clinical outcome at 40 days post presentation with proven meningitis S= survivor NS = Non-survivor. Statistical signficance calculated by Mann-Whitney U test, $p<0.05$ determined statistical signficance.