Abstract Information

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Title :	Brain injury, inflammation, and immunometabolic dysregulation in a murine model of cryptococcal meningitis
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Abstract :

Cryptococcal meningitis is a lethal fungal brain infection caused by the yeast Cryptococcus neoformans. Cryptococcal meningitis has been classified as a neglected tropical disease that disproportionately affects people living with HIV in developing countries. Due to its neglect in research and policy, little is known about the pathogenesis of the disease, especially at the level of the brain. More specifically, the mechanisms underlying the neurological damage associated with death in cryptococcal meningitis patients remain uncharacterized. This study aimed to characterise the neuroimmune response to C. neoformans infection by dissecting host fungal interactions at the cellular and molecular levels.

Male C57BL/6 mice were intravenously injected with 5x104 CFU C. neoformans. At one, three, and six days post-infection, brains were collected for fungal load determination, histopathology, and immunofluorescence analyses. Cellular and molecular responses were characterised using cultured organotypic brain slices treated with 1x10? CFU of a fluorescent reporter strain of C. neoformans. Neuroimmune signalling was determined by tracking nuclear translocation of the pro-inflammatory transcription factor, nuclear factor for interleukin 6 (NF-IL6), and the anti-inflammatory transcription factor, nuclear factor erythroid 2-related factor 2 (NRF2). Multiplex assays for pro- and anti-inflammatory cytokines were performed on blood and brains collected from mice and brain slice culture media. Single-cell RNA sequencing was used for determining cell-type specific transcriptomic responses while bulk metabolomic analyses were carried out to measure metabolic profiles in infected vs uninfected brains.

Our results showed that brain invasion by C. neoformans occurred via the vascular route,

followed by aggregation of the fungus within perivascular spaces before infection of the brain parenchyma and meninges. We observed severe parenchymal lesions (cryptococcomas) formed by yeast aggregates in the cortex, thalamus, midbrain, and cerebellum. Cryptococcal infection was initially associated with limited peripheral and central inflammation, followed by a delayed, injury-related hyperinflammatory response that was accompanied by extensive metabolic dysregulation later during infection.