Abstract Information

First Name :	Rachael
Last Name :	Dangarembizi
Email :	rachael.dangarembizi@uct.ac.za
Address :	Neuroscience Institute, University of Cape Town, South Africa

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Co-Authors :	EMILY HIGGITT, AMALIA AWALA, ANJA DE LANGE, MAAHIR KAUCHALI, LUCIAN DUVENAGE, SUMAYA SALIE, RACHEL LAI, PETER ROSSI-SMITH, JOSEPH RAIMONDO AND JENNIFER HOVING

Abstract :

Fungi have been allies to humanity since the beginning of our existence, aiding in the production of food, beverages, and even treatments for human ailments. However, in recent times, invasive fungal infections have emerged as a significant threat to human health, an adversary for which we currently lack adequate defences.

We study the pathobiology of cryptococcal meningitis; a highly invasive and deadly fungal infection of the central nervous system (CNS) caused by the ubiquitous fungus Cryptococcus neoformans. C. neoformans is a neuroinvasive and neurotropic yeast that is associated with a lethal form of meningoencephalitis (inflammation of the meninges and neural tissue). Patients with CM develop severe neurological damage but the mechanisms driving brain injury in this fatal disease are poorly described.

Using both mouse and human brain tissue models, we have characterized host-fungus interactions at the cellular and molecular levels. We employed single nucleus RNA-sequencing, multiplex assays, and metabolomics analyses to determine the transcriptomic, proteomic and metabolic changes that occur in the brain following infection with C. neoformans. We further investigated neuroimmune signalling in cultured murine and human brain slices and measured cytokine release from infected slices using multiplex cytokine assays.

Our findings reveal that fungi can evade immune destruction in the peripheral system, penetrate the brain via its extensive vascular network, and disrupt neuroimmune balance, resulting in both hypo- and hyperinflammatory responses. This dysregulation leads to injury and neurological damage. We further demonstrate how fungal invasion impairs fluid and waste homeostasis in the brain, exacerbating inflammation and tissue damage.