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Genome-Wide Functional Analysis of the Fungal Pathogenicity Signaling Network

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Past several decades, fungal infections have caused widespread damages to animal and plant ecosystems. It is also reported that about a billion people are estimated to have superficial fungal infections and more than 1.5 million people are killed every year by invasive fungal infections caused by various opportunistic fungal pathogens, such as *Candida*, *Cryptococcus* or *Aspergillus*. Among these, *Cryptococcus neoformans* causes fatal fungal meningoencephalitis, which is responsible for more than 180,000 deaths annually, but its complex signaling networks governing the infection process remain elusive. Over the past few years, we have constructed 155 transcription factor (TF), 129 kinase, and 114 phosphatase mutant libraries in *C. neoformans* and analyzed their *in vitro* and *in vivo* phenotypic traits. Recently, we performed dual signature-tagged mutagenesis (STM)-based murine brain infectivity assay using TF and kinase mutant libraries of the *C. neoformans* H99 strain in comparison with lung STM data and monitored *in vivo* transcription profiles of kinases and TFs during host infection using NanoString technology. These analyses identified many novel signaling components involved in blood-brain-barrier (BBB) adhesion and crossing, or survival in the brain parenchyma. More recently, we have employed human neurovascular organoid chip, which is composed of human brain microvascular endothelial cells, pericytes, astrocytes, and natural brain matrix, and applied it to monitor BBB crossing and neurotropism of *C. neoformans.* Collectively, these efforts will provide further insight into complex signaling networks governing the brain infection and pathogenicity of *C. neoformans*.