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Unravelling of the TOR Signaling Pathway in Human Fungal Pathogen Cryptococcus neoformans

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Abstract : Tor1 is a serine/threonine protein kinase that is widely conserved across eukaryotic species. Tor1 was first identified in Saccharomyces cerevisiae as a target of rapamycin (TOR). The TOR pathway has been implicated in regulating cellular responses to nutrients, proliferation, translation, transcription, autophagy, and ribosome biogenesis. Here we identified two homologues of S. cerevisiae Tor proteins, CNAG_06642 (Tor1) and CNAG_05220 (Tlk1, TOR-like kinase 1), in Cryptococcus neoformans causing a life-threatening fungal meningoencephalitis. Both Tor1 and Tlk1 have rapamycin-binding (RB) domains but Tlk1 has truncated RB form. To study the TOR-signaling pathway in the fungal pathogen, we attempt to construct the tor1Δ and tlk1Δ mutants and phenotypically analyze them. Although we failed to construct the tor1Δ mutant, we successfully construct the tlk1Δ mutant. The tlk1Δ mutant does not exhibit any discernable phenotypes, suggesting that Tlk1 is dispensable in C. neoformans. The essentiality of TOR1 is independently confirmed by constructing the TOR1 promoter replacement strain by using a copper transporter 4 (CTR4) promoter and the TOR1/tor1 heterozygous mutant in diploid C. neoformans strain background followed by sporulation analysis. To further analyze the function of Tor1, we construct TOR1 overexpression mutant using a constitutively active histone H3 in C. neoformans. We find that the Tor1 overexpression mutant is resistant to rapamycin but the tlk1Δ mutant does not exhibit any altered resistance to rapamycin, further confirming that Tor1, but not Tlk1, is critical for TOR signaling. Furthermore, we found that Tor1 is involved in response to diverse stresses, including genotoxic stress, oxidative stress, thermo-stress, antifungal drug treatment, and production of melanin. To identify any TOR-related transcription factors, we screened C. neoformans transcription factor library that we constructed in our previous study and identified several potential downstream factors of Tor1, including Atf1, Crg1 and Bzp3. In conclusion, the current study provides insight into the role of the TOR signaling pathway in human fungal pathogens as well as C. neoformans.

Keywords : fungal pathogen, serine/threonine kinase, target of rapamycin, transcription factor
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