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CAP-Glycine Protein Governs Growth, Differentiation, and the Pathogenicity of Global Meningoencephalitis Fungi

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Abstract : Microtubules are involved in mechanical support, cytoplasmic organization as well as in a number of cellular processes by interacting with diverse microtubule-associated proteins (MAPs), such as plus-end tracking proteins, motor proteins, and tubulin-folding cofactors. A common feature of these proteins is the presence of a cytoskeleton-associated protein-glycine-rich (CAP-Gly) domain, which is evolutionarily conserved and generally considered to bind to α-tubulin to regulate functions of microtubules. However, there has been a dearth of research on CAP-Gly proteins in fungal pathogens, including Cryptococcus neoformans, which causes fatal meningoencephalitis globally. In this study, we identified five CAP-Gly proteins encoding genes in C. neoformans. Among these, Cgp1, encoded by CNAG_06352, has a unique domain structure that has not been reported before in other eukaryotes. Supporting the role of Cpg1 in microtubule-related functions, we demonstrate that deletion or overexpression of CGP1 alters cellular susceptibility to thiabendazole, a microtubule destabilizer, and Cgp1 is co-localized with cytoplasmic microtubules. Related to the cellular functions of microtubules, Cgp1 also governs maintenance of membrane stability and genotoxic stress responses. Furthermore, we demonstrate that Cgp1 uniquely regulates sexual differentiation of C. neoformans with distinct roles in the early and late stage of mating. Our domain analysis reveals that the CAP-Gly domain plays major roles in all the functions of Cgp1. Finally, the cgp1Δ mutant is attenuated in virulence. In conclusion, this novel CAP-Gly protein, Cgp1, has pleotropic roles in regulating growth, stress responses, differentiation and pathogenicity of C. neoformans.

Keywords : human fungal pathogen, CAP-Glycine protein, microtubule, meningoencephalitis
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