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Comparative Functional Analysis of Two Major Sterol-Biosynthesis Regulating Transcription Factors, Hob1 and Sre1, in Pathogenic Cryptococcus Species Complex

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Abstract : Sterol lipid is essential for cell membrane structure in eukaryotic cells. In mammalian cells, sterol regulatory element binding proteins (SREBPs) act as principal regulators of cellular cholesterol which is essential for proper cell membrane fluidity and structure. SREBP and sterol regulation are related to levels of cellular oxygen because it is a major substrate for sterol synthesis. Upon cellular sterol and oxygen levels are depleted, SREBP is translocated to the Golgi where it undergoes proteolytic cleavage of N terminus, then it travels to the nucleus to play a role as transcription factor. In yeast cells, synthesis of ergosterol is also highly oxygen consumptive, and Sre1 is a transcription factor known to play a central role in adaptation to growth under low oxygen condition and sterol homeostasis in Cryptococcus neoformans. In this study, we observed phenotypes in other strains of Cryptococcus species by constructing hob1Δ and sre1Δ mutants to confirm whether the functions of both genes are conserved in most serotypes. As a result, hob1Δ showed no noticeable phenotype under treatment of antifungal drugs and most environmental stresses in R265 (C. gattii) and XL280 (C. neoformans), suggesting that Hob1 is related to sterol regulation only in H99 (serotype A). On the other hand, the function of Sre1 was found to be conserved in most serotypes. Furthermore, mating experiment of hob1Δ or sre1Δ showed dramatic defects in serotype A (H99) and D (XL280). It revealed that Hob1 and Sre1 related to mating ability in Cryptococcus species, especially cell fusion efficiency. In conclusion, HOB1 and SRE1 play crucial role in regulating sterol-homeostasis and differentiation in C. neoformans, moreover, Hob1 is specific gene in Cryptococcus neoformans. It suggests that Hob1 is considered as potent factor-targeted new safety antifungal drug.

Keywords : cryptococcus neoformans, Hob1, Sre1, sterol regulatory element binding proteins
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