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Unique features and function of ER α-1,2-mannosidase homologues in the human fungal pathogen *Cryptococcus neoformans*

Catia Mot , Eun Jung Thak, Su-Bin Lee, an Hyun Ah Kang*
Department of Life Science, Chung-Ang University, Seoul 06974, Republic of Korea

N-glycans play important roles in quality control (QC) of glycoprotein folding in the endoplasmic reticulum (ER) and in ER-associated degradation (ERAD). ER α-1,2-mannosidase I (*MNS1*) contributes to ERQC and ERAD by trimming a mannose residue from the B branch of the *N*-oligosaccharides, initiating the formation of the molecular signals that either lead folded proteins towards the Golgi apparatus, or direct misfolded glycoproteins towards degradation in the cytoplasm (1). The human-pathogen *Cryptococcus neoformans* has a unique *N*-glycosylation lacking ER-associated glucosyltransferases but carrying multiple mannosidases (2). To investigate the molecular assembly of *C. neoformans* specific-glycoprotein QC pathway and its impact on pathogenicity, we disrupted two genes encoding putative ER α-1,2-mannosidases, *MNS1A* and *MNS1B*. The *N*-glycan profiles suggested that, whereas Mns1Ap acts as the widely known ER-α-mannosidase I, Mns1Bp appears to be a novel mannosidase involved in mannose processing in the Golgi. Interestingly, both mannosidases were shown to localize mostly in the Golgi apparatus, as evidenced by the presence of punctate fluorescence patterns resembling golgi stacks. Although the *mns1AD* mutant strain showed only mild growth retardation under several stress conditions, the *mns1BD* displayed the increased sensitivity to high temperature at 39°C and notably increased resistance to SDS. The double mutant strain (*mns1ADmns1BD*) exhibited slightly increased sensitivity to fludioxonil treatment. Moreover, a considerable reduction of capsule mass was observed in both *mns1AD* and *mns1BD*, with the most severe defect in the *mns1ADmns1BD* mutant, suggestive of association with *in vivo* virulence. Overall, our data strongly suggest that the functions of both *MNS1A* and *MNS1B* are involved in proper *N*-glycan processing for glycoprotein QC, which is required for capsule assembly and attachment in *C. neoformans*.

Acknowledgements

This work was supported by the National Research Foundation of Korea grants NRF-2018R1A51102507 and NRF-2019R1A2C1084942.

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*Corresponding author: hyunkang@cau.ac.kr

† These authors contributed equally to this work

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