

Hall, R.A., Bates, S., Lenardon, M.D., MacCallum, D.M., Wagener, J., Lowman, D.W., Kruppa, M.D., Williams, D.L., Odds, F.C., Brown, A.J.P., Gow, N.A.R. (2013). The Mnn2 mannosyltransferases regulate mannoprotein fibril length, immune recognition and virulence of *Candida albicans*. *PLoS Pathogens* **9**(4): e1003276.

The fungal cell wall is the first point of interaction between an invading fungal pathogen and the host immune system. The outer layer of the cell wall is comprised of GPI anchored proteins, which are post-translationally modified by both N- and O-linked glycans. These glycans are important pathogen associated molecular patterns (PAMPs) recognised by the innate immune system. Glycan synthesis is mediated by a series of glycosyl transferases, located in the endoplasmic reticulum and Golgi apparatus. Mnn2 is responsible for the addition of the initial  $\alpha$ 1,2-mannose residue onto the  $\alpha$ 1,6-mannose backbone, forming the N-mannan outer chain branches. In *Candida albicans*, the MNN2 gene family is comprised of six members (MNN2, MNN21, MNN22, MNN23, MNN24 and MNN26). Using a series of single, double, triple, quintuple and sextuple mutants, we show, for the first time, that addition of  $\alpha$ 1,2-mannose is required for stabilisation of the  $\alpha$ 1,6-mannose backbone and hence regulates mannan fibril length. Sequential deletion of members of the MNN2 gene family resulted in the synthesis of lower molecular weight, less complex and more uniform N-glycans, with the sextuple mutant displaying only un-substituted  $\alpha$ 1,6-mannose. TEM images confirmed that the sextuple mutant was completely devoid of the outer mannan fibril layer, while deletion of two MNN2 orthologues resulted in short mannan fibrils. These changes in cell wall architecture correlated with decreased proinflammatory cytokine induction from monocytes and a decrease in fungal virulence in two animal models. Therefore,  $\alpha$ 1,2-mannose of N-mannan is important for both immune recognition and virulence of *C. albicans*.