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FUNGAL PATHOGENESIS

Good copper, bad copper

Copper has long been known for its antimicrobial properties, which have been linked to the production of toxic hydroxyl radicals and the inhibition of Fe–S-dependent enzymes. However, the fungal pathogen *Cryptococcus neoformans* is resistant to copper toxicity, and copper has been implicated in *C. neoformans* virulence. A new study in *Cell Host & Microbe* now clarifies how copper levels influence *C. neoformans* pathogenesis during pulmonary infection.

C. neoformans has a range of copper-responsive genes; some, such as copper transporter 1 (*CTR1*) and *CTR4*, enhance copper acquisition and are induced when the copper supply is limited, whereas others, such as the metallothionein genes *CMT1* and *CMT2*, serve as copper detoxifiers and are induced when copper is in excess. However, it was unclear which condition *C. neoformans* encounters *in vivo*. Using *C. neoformans* reporter strains in which the luciferase gene was under the control of either the *CTR4* or *CMT1* promoter, to allow monitoring of fungal copper-responsive genes in living animals, Ding *et al.* showed that in mouse lungs, expression from the *CMT1* promoter rose steadily after infection, whereas expression from the *CTR4* promoter remained low. This indicates that *C. neoformans* requires copper detoxification during pulmonary infection. In accordance with this, a mutant strain in which both *CMT1* and *CMT2* were deleted produced fewer lung colonies and resulted in less mortality in mice than the wild-type fungus. *In vitro*, the double-mutant strain showed reduced growth in the presence of copper, compared with the wild-type fungus, but normal growth in the presence of other metals. Furthermore, purified Cmt proteins preferentially bound copper rather than other metals, and endogenous Cmt proteins concentrated at the cell periphery, perhaps to trap incoming copper.

> *C. neoformans* requires copper detoxification

Why does *C. neoformans* upregulate copper detoxifiers? To answer this question, Ding *et al.* measured the host copper response. Inductively coupled plasma mass spectrometry showed higher serum copper concentrations in mice infected with *C. neoformans* than in uninfected mice, and immunoblotting revealed that bronchoalveolar lavage cells (which are mostly macrophages) from infected mice produced more of the mouse transporter CTR1 (also known as SLC31A1), which imports copper into the cytoplasm. Usually, macrophages concentrate copper in the phagosome to kill phagocytosed microorganisms. In the macrophages recovered from *C. neoformans*-infected mice, however, the levels of the phagosomal copper importer ATP7A were decreased. Therefore, the authors conclude that the host mounts an antimicrobial copper response after *C. neoformans* infection and the pathogen responds by inhibiting copper accumulation in phagosomes. Further work is required to decipher the precise molecular mechanisms involved.

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ORIGINAL RESEARCH PAPER Ding, C. *et al.* *Cryptococcus neoformans* copper detoxification machinery is critical for fungal virulence. *Cell Host Microbe* **13**, 265–276 (2013)
FURTHER READING Hood, M. I. & Skaar, E. P. Nutritional immunity: transition metals at the pathogen–host interface. *Nature Rev. Microbiol.* **10**, 525–537 (2012)