

Adaptation to thermotolerance in *Rhizopus* coincides with virulence as revealed by avian and invertebrate infection models, phylogeny, physiological and metabolic flexibility.

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Abstract

Mucormycoses are fungal infections caused by the ancient Mucorales. They are rare, but increasingly reported. Predisposing conditions supporting and favoring mucormycoses in humans and animals include diabetic ketoacidosis, immunosuppression and haematological malignancies. However, comprehensive surveys to elucidate fungal virulence in ancient fungi are limited and so far focused on *Lichtheimia* and *Mucor*. The presented study focused on one of the most important causative agent of mucormycoses, the genus *Rhizopus* (*Rhizopodaceae*). All known clinically-relevant species are thermotolerant and are monophyletic. They are more virulent compared to non-clinically, mesophilic species. Although adaptation to elevated temperatures correlated with the virulence of the species, mesophilic strains showed also lower virulence in *Galleria mellonella* incubated at permissive temperatures indicating the existence of additional factors involved in the pathogenesis of clinical *Rhizopus* species. However, neither specific adaptation to nutritional

requirements nor stress resistance correlated with virulence, supporting the idea that Mucorales are predominantly saprotrophs without a specific adaptation to warm blooded hosts.

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