Hitting the caspofungin salvage pathway of human-pathogenic fungi with the novel lasso peptide humidimycin (MDN-0010).

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Abstract

Fungal infections have increased dramatically in the last two decades and fighting infectious diseases require innovative approaches such as the combination of two drugs acting on different targets, or even target a salvage pathway of one of the drugs. The fungal cell wall biosynthesis is inhibited by the clinically used antifungal drug caspofungin. This antifungal activity has been found to be potentiated by humidimycin, a new natural product identified from the screening of a collection of 20,000 microbial extracts and with no major effect when used alone. The analysis of transcriptomes and selected *A. fumigatus* mutants indicated that humidimycin affects the high osmolarity glycerol response pathway. By combining humidimycin and caspofungin a strong increase of caspofungin efficacy was achieved, demonstrating that targeting different signaling pathways provides an excellent basis to develop novel anti-infective strategies.

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