Network Modeling Reveals Cross Talk of MAP Kinases during Adaptation to Caspofungin Stress in *Aspergillus fumigatus*.

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Details



Abstract

Mitogen activated protein kinases (MAPKs) are highly conserved in eukaryotic organisms. In pathogenic fungi, their activities were assigned to different physiological functions including drug adaptation and resistance. *Aspergillus fumigatus* is a human pathogenic fungus, which causes life-threatening invasive infections. Therapeutic options against invasive mycoses are still limited. One of the clinically used drugs is caspofungin, which specifically targets the fungal cell wall biosynthesis. A systems biology approach, based on comprehensive transcriptome data sets and mathematical modeling, was employed to infer a regulatory network and identify key interactions during adaptation to caspofungin stress in *A. fumigatus*. Mathematical modeling and experimental validations confirmed an intimate cross talk occurring between the cell wall-integrity and the high osmolarity-glycerol signaling pathways. Specifically, increased concentrations of caspofungin

promoted activation of these signalings. Moreover, caspofungin affected the intracellular transport, which caused an additional osmotic stress that is independent of glucan inhibition. High concentrations of caspofungin reduced this osmotic stress, and thus decreased its toxic activity. Our results demonstrated that MAPK signaling pathways play a key role during caspofungin adaptation and are contributing to the paradoxical effect exerted by this drug.

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