Induction of Mitochondrial Reactive Oxygen Species Production by Itraconazole, Terbinafine, and Amphotericin B as a Mode of Action against *Aspergillus fumigatus*.

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Abstract

Drug resistance in fungal pathogens is of incredible importance to global health, yet the mechanisms of drug action remain only loosely defined. Antifungal compounds have been shown to trigger the intracellular accumulation of reactive oxygen species (ROS) in human-pathogenic yeasts, but the source of those ROS remained unknown. In the present study, we examined the role of endogenous ROS for the antifungal activity of the three different antifungal substances itraconazole, terbinafine, and amphotericin B, which all target the fungal cell membrane. All three antifungals had an impact on fungal redox homeostasis by causing increased intracellular ROS production. Interestingly, the elevated ROS levels induced by antifungals were abolished by inhibition of the mitochondrial respiratory complex I with rotenone. Further, evaluation of lipid peroxidation using the thiobarbituric acid assay revealed that rotenone pretreatment decreased ROS-induced lipid peroxidation during incubation of *Aspergillus fumigatus* with itraconazole and terbinafine. By applying the mitochondrion-specific lipid peroxidation probe MitoPerOx, we also

confirmed that ROS are induced in mitochondria and subsequently cause significant oxidation of mitochondrial membrane in the presence of terbinafine and amphotericin B. To summarize, our study suggests that the induction of ROS production contributes to the ability of antifungal compounds to inhibit fungal growth. Moreover, mitochondrial complex I is the main source of deleterious ROS production in *A. fumigatus* challenged with antifungal compounds.

Beteiligte Forschungseinheiten

Molekulare und Angewandte Mikrobiologie Axel Brakhage Mehr erfahren

Leibniz-HKI-Autor*innen



Axel A. Brakhage

Details



Olaf Kniemeyer

Details



Elena Shekhova

Details

Identifier

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