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Antifungal compounds redirect metabolic pathways in yeasts: metabolites as indicators of modes of action

J. Wesolowski*, R.Y.A. Hassan*, K. Reinhardt, S. Hodde and U. Bilitewski
Helmholtz Centre for Infection Research, Research Group Biological Systems Analysis, Inhoffenstr.,
Braunschweig, Germany

Abstract:

Aims: Metabolic pathways, e.g. biosynthesis of ergosterol or carbohydrate metabolism including respiration, are well-known targets of several fungicides. With our study we wanted to prove that metabolite profiles can be used to classify fungicides according to their mode of action and that concentrations of key metabolites are changed even without detectable reduced growth rates.

Methods and Results: We exposed the yeasts *Candida albicans* and *Saccharomyces cerevisiae* to inhibitors of the electron transport chain and to compounds known to interact with osmotic stress defence pathways. Glycerol and ethanol were chosen as key metabolites of branches of glucose catabolism. Increased glycerol concentrations were observed not only when the osmotic stress response was activated, but also as response to the inhibition of the electron transfer chain, whereas elevated ethanol levels were observed only when the respiratory pathways were blocked.

Conclusions: The treatment of the yeasts *Candida albicans* and *Saccharomyces cerevisiae* with antimycotic compounds led to a redirection of metabolic pathways, which could be followed by the quantification of both the metabolites ethanol and glycerol. Only the combination of both concentration profiles allowed the clear distinction between inhibitors of the respiratory chain and effects on the osmotic stress response pathway.

Impact of Study: The extension of the number of metabolites to a comprehensive quantitative metabolic profile of compound-treated test organisms can be an additional tool in fungicide research allowing the detection of compounds which act on fungi and, moreover, the elucidation of modes of action

Key-words: Ambruticin VS-3, *Candida albicans*, fludioxonil, glycerol, myxothiazol, pyrrolnitrin