Proteomic profiling of the antifungal drug response of *Aspergillus fumigatus* to voriconazole.

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Abstract

Antifungal resistance is an emerging problem and one of the reasons for treatment failure of invasive aspergillosis (IA). Voriconazole has become a standard therapeutic for the treatment of this often fatal infection. We studied the differentially expressed proteins as a response of *Aspergillus fumigatus* to voriconazole by employing the two-dimensional difference gel electrophoresis (DIGE) technique. Due to addition of drug, a total of 135 differentially synthesized proteins were identified by MALDI-TOF/TOF-mass spectrometry. In particular, the level of proteins involved in the general stress response and cell detoxification increased prominently. In contrast, cell metabolism and energy proteins were down-regulated, which suggests the cellular effort to maintain balance in energy utilization while trying to combat the cellular stress exerted by the drug. We detected several so-far uncharacterized proteins which may play a role in stress response and drug metabolism and which could be future targets for antifungal treatment. A mutant strain, which is deleted in the cross-pathway control gene cpcA, was treated with voriconazole to investigate the contribution of the general control of amino acid biosynthesis to drug resistance. We compared the

mutant strain's protein expression profile with the wild-type strain. The absence of CpcA led to an increased resistance to voriconazole and a reduced activation of some general stress response proteins, while the transcript level of the triazole target gene erg11A (cyp51A) remained unchanged. In contrast, the sensitivity of strain ΔcpcA to terbinafine and amphotericin B was slightly increased. These findings imply a role of CpcA in the cellular stress response to azole drugs at the post transcriptional level.

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