A role for iron-sulfur clusters biogenesis in fluconazole tolerance

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Doxycycline was found to act synergistically with the antifungal fluconazole against Candida albicans as well as against Saccharomyces cerevisiae (1). Combination with doxycycline converts fluconazole from fungistatic to fungicidal and prevents the onset of drug resistance. This synergism may be accounted for by doxycycline-mediated iron titration, since growth inhibition can be reversed by externally added iron. However, the mechanism by which iron depletion synergizes with fluconazole is not clear.

We isolated MGE1 as a gene capable to restore tolerance to fluconazole in cells of baker’s yeast, when overexpressed. Mge1, the yeast homolog of the bacterial GrpE co-chaperone, is a mitochondria-resident nucleotide exchange factor with a double role. On one side, Mge1 promotes the release of ADP from the Ssc1 chaperone to allow ATP-dependent translocation of cytoplasmically-synthesized proteins to mitochondria. On another side, Mge1 works as a nucleotide release factor for Ssq1, a mitochondrial chaperone promoting the correct folding of proteins containing iron-sulfur clusters.

Using a conditional mutant allele of MGE1 which confers a temperature-sensitive phenotype (2), we found that the suppressing activity relies on interaction of Mge1 with chaperone Ssq1, thereby restricting the activity of Mge1 in iron-sulfur clusters biogenesis as the suppressing one. MGE1-mediated suppression does not synergize with suppression mediated by another multicopy suppressor, ERG11, encoding the protein target of fluconazole (1). This result indicates that both proteins’ activities probably converge on the same pathway; consistently, overexpression of MGE1 was found to stabilize Erg11 in response to fluconazole and fluconazole+doxycycline, while not altering ERG11 expression.

Evidence for a role of the C. albicans Mge1 homolog in fluconazole tolerance is also being gathered and will be presented at the meeting.

Keywords Candida albicans; fluconazole; iron; iron-sulfur clusters.

References
