Fluconazole Exposure Induces Genotypic and Phenotypic Changes in Candida glabrata

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Candida glabrata is recognized as a leading fungal pathogen of mucosal and systemic infections in compromised individuals, second only to C. albicans. One reason for this is the widespread use of fluconazole which leads to emergence of fluconazole resistant strains in C. glabrata. Objectives: To obtain a fluconazole resistant C. glabrata strain with sequential, repeat exposure to fluconazole in vitro and determine its genotypic and phenotypic attributes. Methods: C. glabrata ATCC 2001 was cultured in Sabourauds dextrose agar and exposed repeatedly to RPMI medium laced with fluconazole (×2MIC) for a continuous period of 43 days. Molecular data of the drug exposed Candida strain was compared with the control yeast, using randomly amplified polymorphic DNA (RAPD) and, pulsed-field gel electrophoresis (PFGE) of chromosomal DNA treated with restriction endonuclease SfiI. Fluconazole MIC changes were evaluated using the E-test (AB Biodisk; Kalvagen, Solna, Sweden), cell viability monitored using both the ATP bioluminescence and conventional colony forming unit assays and phenotypic switching monitored in RPMI/16µg/ml fluconazole. Results: After drug exposure for 11 days, there was an increase in the MIC from 8µg/ml to 64µg/ml, with fluctuating cell viability and a reduction in total cell yield (from 1.0 - 0.6 × 10^4 cells/ml). A strong positive correlation between the ATP and CFU counts (r = 0.8556; p<0.001) was also noted. Phenotypic switching of C. glabrata was observed after 36 days at a frequency of 1.6% and significant changes in the chromosomal DNA profile was observed after 43 days of drug exposure. Conclusion: Chromosomal DNA changes as well as phenotypic changes in C. glabrata may occur due to sequential exposure of this yeast to fluconazole. (Supported by the Research Grants Council and the Committee of Research and Conference grants (a/c 10205959) of the University of Hong Kong, Hong Kong SAR.)

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