NAME: Edwina Thomas

SUPERVISOR: Dr. Nikhat Manzoor

CO-SUPERVISOR: Dr. Sneh Lata Bhadoriya

DEPARTMENT: DEPARTMENT OF BIOSCIENCES, JAMIA MILLIA ISLAMIA

Title: Role of Mitochondria in Multidrug Resistance in *Candida albicans*

ABSTRACT

Broad Area of Research: Yeast Molecular Genetics

Specific Area of Research: Multidrug resistance in *C. albicans*

Keywords: *Candida albicans*, azoles, MDR, phospholipid, ergosterol, Hog1, iron homeostasis

C. albicans is a dimorphic fungus, which means that it exists in both yeast and hyphal forms. *Candida* species are ubiquitous in nature and more than 100 species of *Candida* are known but only a few species are recognized as disease causing in humans. *C. albicans* is an opportunistic fungus which is extensively isolated from patients suffering from invasive candidiasis. Among several classes of antifungals, azole group of drugs like ketoconazole and itraconazole have been recognized as the most commonly used fungicide in the treatment of *Candida* infections. This phenomenon is called as **M**ultiple **D**rug **R**esistance (MDR) which can be defined as resistance of an organism against a spectrum of drugs that share neither a common target nor a common structure.

Mitochondrial dysfunction in *C. albicans* is known to be associated with drug susceptibility, cell wall integrity, phospholipid homeostasis and virulence. In this study, we deleted *CaFZO1,* a key component required during biogenesis of functional mitochondria. Cells deleted of *FZO1* displayed fragmented mitochondria, mitochondrial genome loss, reduced mitochondrial membrane potential and were

rendered sensitive to azoles and peroxide. In order to understand the cellular response to dysfunctional mitochondria, genome-wide expression profiling of *fzo1*Δ/Δ cells was performed. Our results show that the increased susceptibility to azoles was likely due to reduced efflux activity of *CDR* efflux pumps, caused by the missorting of Cdr1p into the vacuole. Genome wide transcription analysis showed that the major effects of dysfunctional mitochondria were (a) a much larger set of 649 genes was down regulated and (b) a co-regulated response of genes involved in specific biological processes was triggered.Additionally, *fzo1*Δ/Δ showed up regulation of genes involved in iron assimilation, in iron sufficient conditions, characteristic of iron starved cells. Cellular iron content in the mutant was also significantly higher in the mutant compared to the wild type. One of the consequent effects was down regulation of genes of the ergosterol biosynthesis pathway with a commensurate decrease in cellular ergosterol levels. We therefore connect de-regulated iron metabolism to ergosterol biosynthesis pathway in response to dysfunctional mitochondria. Impaired activation of the Hog1 pathway in the mutant was the basis for increased susceptibility to peroxide and increase in ROS, indicating the importance of functional mitochondria in controlling Hog1-mediated oxidative stress response. Mitochondrial phospholipid levels were also altered as indicated by an increase in phosphatidylserine and phosphatidylethanolamine and decrease in phosphatidylcholine in *fzo1*Δ/Δ cells. While the cell wall integrity pathway was found to be intact in *fzo1*Δ/Δ, susceptibility to certain cell wall damaging agents such as caspofungin, tunicamycin and detergent, SDS was increased. The observed susceptibility may be due to changes in the cell wall composition, particularly chitin content.Collectively, these findings reinforce the connection between functional mitochondria and azole tolerance, oxidant mediated stress and iron homeostasis in *C. albicans*.