SUMMARY

Candida albicans is an opportunistic pathogen able to colonize and infect the hosts, causing mucosal infections which weaken the body as well as life-threatening systemic infections. One of the mechanisms by which *C. albicans* cells adapt to colonize the host organism is high genetic variability, including observed at the chromosome level. The chromosomal variability of *C. albicans* cells is often associated with mass genomic rearrangements, including changes in cell ploidy. Genomic rearrangements lead to the generation of cells with a changed phenotype within the *C. albicans* population, providing them with a significant advantage during infection relative to the cells of the starting population. Dynamics of genome reorganization of *C. albicans* may be significantly modified by the presence of different exogenous factors. The source of genetic variation can be drugs, chemicals agents, as well as reactive oxygen and nitrogen species produced by host cells during infection. Therefore, the best understanding of the factors modifying chromosomal variability, taking into account their mechanisms of action on *C. albicans* cells, is one of the major challenges of modern science, which is of great importance for the development of new therapeutic strategies.

The aim of the doctoral dissertation was to evaluation of the role of non-enzymatic post-translational protein modifications in promoting intercellular chromosomal variation in *C. albicans*. In particular, the significance of non-enzymatic post-translational protein modifications in the process of chromosomal heterogenization of the population of chronologically aging *C. albicans* cells was assessed. As part of the study, clastogenic and aneugenic properties of selected compounds generating a specific type of protein modification such as methylglyoxal, hydrogen peroxide, sodium hypochlorite and nitric oxide donor - DPTA were analyzed. Additional effect of fluconazole, the most commonly used drug during infection on chromosomal instability and level of non-enzymatic post-translational protein modifications was described.

During this study the following strains of *C. albicans* were used: ATCC14053, SC5314 as well as 4 clinical strains of *C. albicans* (302, T2, T6, T15). Additionally, a new innovative method was developed using specific oligonucleotide genetic probes painting chromosomes as a unique tool for studying intercellular variability at the level of a single cell. The genetic characterization of selected strains showed variability at the level of karyotype patterns and DNA content in the *C. albicans* nucleus. The analyses also proved that the tested strains are

characterized by a variable ability to accumulate non-enzymatic post-translational modifications of proteins (carbonylation, glycation, nitration, chlorination), as well as variability of genomic instability dependent on ploidy level, among others chromosomal aberrations, DNA strand breaks, including the formation of replication intermediates.

The obtained results also showed that the frequency of chromosomal changes and the formation of non-enzymatic post-translational modifications in *C. albicans* cells may depend on the culture time (chronological age of the cells), as well as the stress factor used. Changes in the levels of DNA and protein damage by endo- and exogenous factors promote intercellular variability and affect the adaptability of cells under stress, including the action of azole drugs.

The obtained results indicate the need for a new rational therapeutic approach in the fight against opportunistic *C. albicans* infections, including the use of combined therapy based on combined azole drugs with senolytic compounds. The results also confirm the existence of a serious problem associated with widely used antifungal compounds, including surfactants such as hypochlorite, hydrogen peroxide, which, in addition to cytotoxic activity, may also promote intercellular variation among *C. albicans*.

Additionally, new biotechnological tools have been developed, namely genetic probes *in situ* for the study of *C. albicans* chromosomes at the individual cell level that may supplement current methodologies and techniques for studying the *C. albicans* genome in the future.

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