Extended Abstract
Volume 5:6, 2021

Journal of Genetics and DNA Research

Open Access

Screen of RNA aptamers to target CHS5 chitin trafficking signal as anti-fungal

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Abstract

Chitin is a glycan composed of 1, 4-linked N-acetyl-D-glucosamine that exist in cell wall of Saccharomyces cerevisiae (S. cerevisiae). One of the emerging fungal pathogens is S. cerevisiae, when host defenses are weakened. S. cerevisiae strains show a specific transcription pattern after human blood infection and sequencing of genomes in yeast and mammals that encode very similar proteins. They make systemic infection and even death in the worst scenarios. In this work, in silico approach to screening RNA with potential binding affinity to a desired Chs5 (Chitin localization protein agent) to block chitin transferred. Atom coordinate of Chs5 were extracted from one of the conformations which had been determined by solution nuclear magnetic resonance (NMR) spectroscopy (PDB accession code: 4WJW). Aptamer were extracted from protein data bank Europe. Screening was performed using the Chimera program to prepare ligands and receptor for dock. The calculation procedure for aptamers and receptor was using dock 6.7. For a better understanding of docking structures, the best positions of interaction of aptamer on S. cerevisiae protein were monitored. All structures with low level of energy were extracted and visualized by PyMol. In this present work, I will discuss aptamer inhibitor against S. cerevisiae as antibiotic; more about how aptamer can more specific target protein than antibody, also, about similar genome of S. cerevisiae with human and why this friendly yeast has become dangerous to human body.

Fungal infection is a leading cause of mortality in immunocompromised population; thus, it is urgent to develop new and safe antifungal agents. Different from human cells, fungi have a cell wall, which is composed mainly of polysaccharide glucan and chitin. The unique cell wall structure is an ideal target for antifungal drugs. In this research, a chemical-genetic method was used to isolate antifungal agents that target chitin synthesis in yeast cells. From a compound library, we isolated two benzothiazole compounds that showed greater toxicity to yeast mutants lacking glucan synthase Fks1 compared to wild-type yeast cells and mutants lacking chitin synthase Chs3. Both of them inhibited the activity of chitin synthase in vitro and reduced chitin level in yeast cells. Besides, these compounds showed clear synergistic antifungal effect with a glucan synthase inhibitors caspofungin. Furthermore, these compounds inhibited the growth of Saccharomyces cerevisiae and opportunistic pathogen Candida albicans. Surprisingly, the genome-wide mass-spectrometry analysis showed decreased protein level of chitin synthases in cells treated with one of these drugs, and this decrease was not a result of downregulation of gene transcription. Therefore, we successfully identified two new antifungal agents that inhibit chitin synthesis using a chemical-genetic method.

This work is partly presented at International Conference on Glycobiology