CALIFORNIA STATE SCIENCE FAIR
2015 PROJECT SUMMARY

Name(s)

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Project Number

35301

Project Title

Transcriptional Regulators as Drug Targets for Treatment of C. glabrata Infection

Abstract

Objectives/Goals

1) Discover transcriptional regulators of the fungus Candida glabrata that govern resistance to antimicrobial peptides and the antifungal drug caspofungin, 2) test the virulence of C. glabrata transcription factor deletion mutants that are sensitive to both antimicrobial peptides and caspofungin in the Galleria mellonella model, 3) identify potential antifungal drugs that inhibit these transcriptional regulators.

Methods/Materials

Screen library of 216 C. glabrata transcription factor deletion mutants by plating serial 10-fold dilutions of each mutant and the wild-type strain onto agar containing the antimicrobial peptide protamine or caspofungin. Use bioinformatics to determine the function of transcriptional regulators that were found to govern resistance to protamine and caspofungin. Adapt G. mellonella model of disseminated C. glabrata infection to test virulence of the transcription factor mutants, using survival as the endpoint. Use computer-assisted modelling, docking, and screening to identify potential antifungal drugs.

Results

Last year, 91 mutants were screened, identifying 3 transcriptional regulators that formed the SAGA histone acetyltransferase complex. This year, an additional 125 mutants were screened, identifying 6 mutants that were sensitive to both protamine and caspofungin. Bioinformatics showed that 3 transcriptional regulators formed the RPD3L histone deacetylase complex and the COMPASS histone methyltransferase complex. These complexes and the previously discovered SAGA complex govern expression of resistance genes by modifying histones. Virulence studies in G. mellonella showed that only the transcriptional regulator Ada2 of the SAGA complex was required for virulence. Computer screening identified sulfonamides as potential inhibitors of Ada2.

Conclusions/Discussion

The RPD3L, COMPASS, and SAGA complexes govern resistance by modifying histones, indicating that histone modification is a key mechanism by which C. glabrata resists antimicrobial peptides and caspofungin. Because Ada2 is important for both resistance and virulence, it is a promising drug target. Computer modelling and screening identified sulfonamides as potential Ada2 inhibitors. Because sulfonamides are already used to treat bacterial and parasitic infections in humans, they are promising antifungal drugs.

Summary Statement

In Candida glabrata, the transcriptional regulator Ada2 of the SAGA histone acetyltransferase complex is required for both resistance and virulence, is a promising drug target, and is likely inhibited by sulfonamide drugs.

Help Received

Used lab equipment at the Los Angeles Biomedical Research Institute under the supervision of Dr. Edwards.