In silico Investigation of Biophysical Relationships Between a Unique Codon Reassignment and Morphological Plasticity in Candida Fungal Pathogens of the CTG Clade

Hatton, Eli (School: Rowland Hall- Lincoln Street Campus)

Pathogenic fungi of the Candida genus, including C. albicans, pose an increasing threat to global health. Almost all Candida species belong to the CTG clade, which deviates from the common genetic code by translating serine at CUG codons instead of leucine. Notably, C. albicans can switch rapidly between biofilm and yeast-like growth states, and must do so to be virulent. The goal of this study was to elucidate a potential biophysical relationship between serine translation at the CUG codon and morphological plasticity. A set of proteins selected based on their critical involvement in morphological switching and the presence of high proportions of CUG codons (especially in functionally important domains), were modeled in-silico to investigate their dependence on serine at CUG residues for structure and function. Structures for each protein were predicted using the AlphaFold AI model, mutated to leucine at CUG residues, and compared to wild-type structures through a series of in-silico assays to evaluate the structural and functional implications of the mutations. Evaluated metrics included thermodynamic data for protein folding, internal interactions, and protein-ligand interactions. Static analysis included solubility changes, binding sites, and predicted biological function. Molecular dynamics simulations of the structure of proteins over time and docking analysis for ligands were applied. Five of the original 13 proteins were found to have significant disruptions in structure and function due to mutation, suggesting that they may depend on serine incorporation. These five proteins are promising candidates for in-vitro validation. This study opens up future research for novel therapeutic approaches, including using exogenous tRNA to force leucine misincorporation.

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