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SEARCH STRATEGY OF NEW ANTIFUNGAL TARGETS BASED ON ANALYSIS OF THE PROTEIN DOMAIN AND DOMAIN ARCHITECTURE CONTENT OF FUNGAL PROTEOMES.

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OBJECTIVES: Over the past several years fungal infections have shown an increasing incidence in the susceptible population, and caused high mortality rates. In parallel, multiresistant fungi are emerging in human infections. Therefore, the identification of new potential antifungal targets is a priority. In this study we analyse the protein domain and domain architecture content of the 137 fungal genomes (corresponding to 111 species) with the aim of finding potential targets for new antifungal drugs.

METHODS: 137 fungal proteomes (those present in UniProtKB release 2013_01) were analyzed The related domain information was retrieved from the Pfam database release 27.0. All the information was stored in a local MySQL database. In addition, the same information was retrieved from the human proteome, for comparison purposes. Three different approaches were used to look for potential antifungal drugs targets: (i) Identify those domains/domain architectures present in fungi and not present in the human proteome; (ii) identify fungal promiscuous domains and determine the pathways where the proteins containing these domains could be involved; and (iii) Look for exclusive domains in the more clinically relevant fungal species, and determine which of them had the potential to bind small molecules.

RESULTS: The 137 fungal proteome sets represented 111 species of the following five fungal phyla: Ascomycota, Basidiomycota, Chytridiomycota, Zygomycota and Microsporidia. Overall, 1,191,070 proteins were analysed, with an average size of 8,694 proteins per proteome. A total of 5,279 different Pfam domains were found among the studied proteomes (35.6% of the total Pfam domains). Among them, 131 domains (2.5%) were found in every fungus analysed. Of the total domains analysed, 1,786 domains and 13,111 domain architectures were found only in fungi and not present in the human proteome. The resulting list of core and exclusive domain and domain architectures was analysed at the different levels of fungal taxonomic classification: phylum, subphylum, order, genus, and species. . Three pathways were identified as enriched with promiscuous domains in the species studied: lovastatin biosynthesis, xylan degradation and siroheme biosynthesis. In a previous study, a list of 215 Pfam domains was generated where evidence of ligand-binding capabilities to small molecules was found. Seven of these domains were exclusive for one group of clinical isolates that included some multiresistant species such as *Fusarium oxysporum* and *Rhizopus delemar* (closely related to *Rhizopus oryzae).*

CONCLUSIONS: In this study, we have characterized the protein domain and domain architecture content of the available fungal proteomes and we have shown how that information can be used *in silico* to detect potential candidate targets for antifungal drugs. These approaches could also be used for organisms with clinical interest other than fungi.