Search strategy of new antifungal targets based on analysis of the protein domain and domain architecture content of fungal proteomes

eP392

Alejandro Barrera [1,2], Ana Alastruey-Izquierdo[2], María J. Martín[1], Juan Antonio Vizcaíno[1] & Isabel Cuesta[2]

[1] European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SD, UK.
[2] National Centre for Microbiology, Instituto de Salud Carlos III, Majadahonda, Madrid, 28020, Spain.

Introduction: Over the past several years fungal infections have shown an increasing incidence in the susceptible population, with associated 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.

Materials and Methods

A total of 137 fungal proteomes (UniProtKB release 2013_01) were analysed. 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.

Results

The relationship between the number of Pfam-A domains and the number of architectures is approximately linear. However, filamentous fungi generally tend to have a large ratio of architectures by domains; on the contrary yeasts have more domains than architectures (Figure 1).
Filamentous fungi like *Aspergillus* have the largest number of specific architectures with a handful unique domains (Figure 2). In contrast, ancient species like *Enterocytozoon* have an average number of architectures with several exclusive domains.

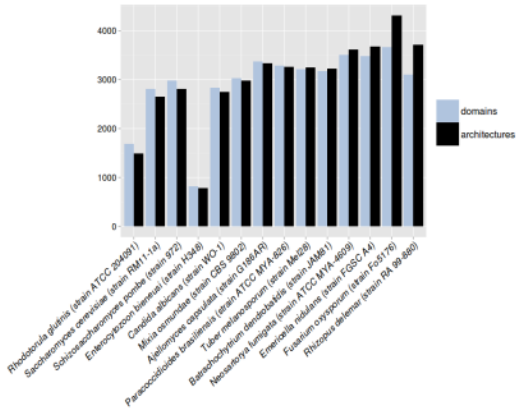

Figure 1. Distribution of number of Pfam domains and architectures found for selected species.

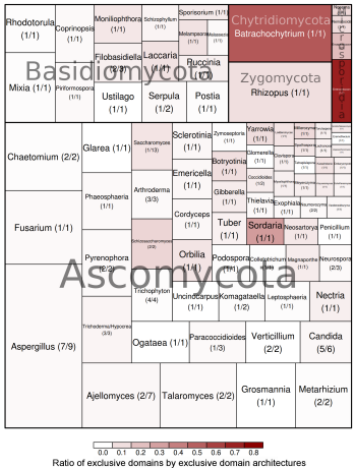

Figure 2. Distribution of Pfam domains and domain architectures per genus.

The number of domains and domain architectures either unique or shared between human and fungi are represented in Figure 3.
Of 219 fungal promiscuous domains, eight of them were not found in the human proteome. Three pathways present in UniPathway were identified as potential targets for antifungals: Lovastatin biosynthesis, Xylan degradation and Biosynthesis of siroheme.
For clinically relevant species 13 exclusive domains were found. Among those domains, 'HI0933_like', 'TIR_2', and 'Keratin_B2_2' can be highlighted .

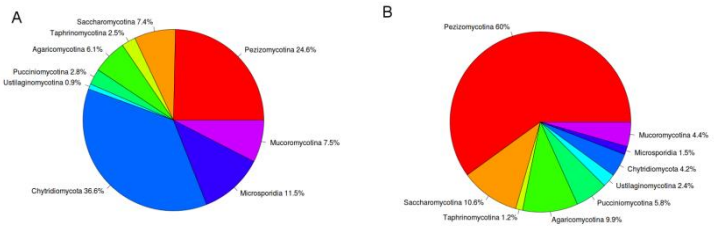

Figure 4. Distribution of protein domains (A) and domain architectures (B), exclusively found in the different fungal subphyla.

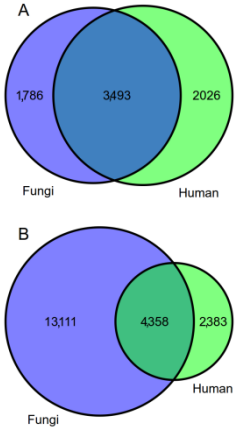

Figure 3. Distribution of protein domains (A), domain architectures (B) shared between the fungal species and *Homo sapiens.*

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.

Contact information: Ana Alastruey-Izquierdo: anaalastruey@isciii.es
Barrera *et al.* Analysis of the protein domain and domain architecture content in fungi and its application in the search of new antifungal targets ***PLOS Comp Biol*** (Under review)