GENE CONSERVATION, DUPLICATION AND THE EVOLUTION OF NATURAL MULTIDRUG RESISTANCE IN FUNGI

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Bacterial drug resistance is a topic of great concern to the scientific community and a major threat to public health. However, few studies have systematically addressed fungal multidrug resistance using genome-wide datasets. Here we assembled a large compendium of *Saccharomyces cerevisiae* chemogenomic data to study the evolution of multidrug resistance genes (MDRs) in Fungi. We found that MDRs generally evolve in conserved families; most of which containing homologs from pathogenic Fungi, such as *Candida albicans* and *Coccidioides immitis*, which could favor the emergence of drug resistance in these species. By integrating chemogenomic data with protein family conservation and protein/genetic interaction patterns, we found that gene families rarely have more than one MDR, indicating that paralogs evolve asymmetrically with regard to drug resistance roles. Furthermore, MDRs have more genetic and protein interaction partners than non-MDRs, supporting their participation in complex biochemical systems underlying the tolerance to multiple bioactive molecules. MDRs share more chemical genetic interactions with each other than they do with non-MDRs, regardless of sequence similarity. This support the existence of an intricate biochemical system involved in the drug tolerance phenotypes. Finally, MDRs are more frequently hit by mutations in laboratory evolution experiments, supporting their adaptive potential in fungal evolution to fluctuating and harsh environments. Our results uncover major genomic features underlying MDRs evolution and shed light on the gene families from which drug resistance is more likely to emerge in Fungi.

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