Chapter XXIV
Systems Biology of Human–Pathogenic Fungi

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ABSTRACT

This chapter describes a holistic approach to understand the molecular biology and infection process of human-pathogenic fungi. It comprises the whole process of analyzing transcriptomic and proteomic data. Starting with biological background, information on Aspergillus fumigatus and Candida albicans, two of the most important fungal pathogens, is given. Afterwards, techniques to create transcriptome and proteome data are described. The chapter continues with explaining methods for data processing and analysis. It shows the need for, and problems with data integration, as well as the role of standards, ontologies, and databases. General aspects of these 3 major topics are explained and connected to the research on human-pathogenic fungi. Finally, the near future of this research topic is highlighted. This chapter aims to provide an overview on analyses of data from different cellular levels of human-pathogenic fungi. It describes their integration and application of systems biology methodologies.

INTRODUCTION

In the past, biologists mostly studied one or few genes or gene products at a time. In recent years, it was realized that it is not enough to understand the basic elements of a system. It is also necessary to understand the system as a whole. Systems biology is a holistic, cross-disciplinary approach of studying biological systems (Ideker, Galitski, & Hood, 2001). It considers organisms and their environment as series of hierarchical levels. Systems biology can be divided into two branches. Bottom-up approaches, which aggregate detailed knowledge of single components and their interactions into suitable modules, are the first one. The second branch are top-down approaches, which decompose global data to gain knowledge of smaller modules. Bottom-up approaches are most important in research on human-pathogenic fungi at present. They work by systematically perturbing the biological system under study, monitoring the response, integrating data, and finally modelling the biological process. Iteratively, experiments are made to validate the model and the model is refined to fit experimental findings.

A completely sequenced genome of an organism is the framework of any global approach. Together with transcriptomic and proteomic data, it builds the foundation for systems biology (Aggarwal & Lee, 2003). For several human-pathogenic fungi, including *Aspergillus fumigatus* and *Candida albicans*, the genome has been sequenced. Several studies have been conducted using 'omics' methodologies and storing results in databases. This chapter wants to provide insight into current work that is done on different cellular levels of human-pathogenic fungi and the state of systems biology research in this area.

BACKGROUND

Mycoses

Experts believe that 1.5 million fungal species exist. Only 100-150 of them are associated with human infections. First human mycoses were discovered in the middle of the 19th century. In the last two decades, the number of patients suffering from invasive forms of fungal infections has grown rapidly. Today, *A. fumigatus* and *C. albicans* are the two major causes of such invasive diseases (Kullberg & Oude Lashof, 2002). Main reason for this development is the rising number of immunocompromised patients that are mostly affected by opportunistic pathogens. Humans that undergo immunosuppressive therapy, transplantations, intensive care or massive surgeries as well as humans infected with HIV are most susceptible. In addition, aging of the population and increased survival chances for premature newborns have increased the number of endangered persons. The investigation of the infection process on molecular level will help to reduce the risk of disease for these groups of people.

In very recent times, molds other than *A. fumigatus (e.g., A. flavus, A. terreus)* and yeasts other than *C. albicans* (e.g., *C. glabrata, C. tropicalis)* emerged as human pathogens (Kullberg & Oude Lashof, 2002; Nucci & Marr, 2005). Also, other fungal species, for example *Coccidioides posadasii* or *Cryptococcus neoformans*, cause mycoses in humans. These fungi are far less common, so this chapter is mainly restricted to *A. fumigatus* and *C. albicans*.

Aspergillus Fumigatus

Aspergillus fumigatus was first described and characterized by J. B. G. W. Fresenius in 1863. It is the primary mold pathogen and most important airborne fungal pathogen. The fungus can be found in soil

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