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Functional Genomics of *Candida albicans*

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The human fungal pathogen *Candida albicans* is a normal part of the microflora in the gastrointestinal tract, mouth and genital tract. It causes not only superficial infections, but also life-threatening disease in individuals with immune system defects [1]. With the growth of the immunocompromised patient population due to the prevalence of AIDS and advanced technologies of medical therapies, fungal infections caused by *Candida* species have dramatically increased over the past decades [1,2]. Great progresses have been made in exploring the biological and pathogenic features of *C. albicans* since the publication of the complete genome sequence of SC5314, a laboratory strain of *C. albicans* in 2000 [3,4]. The availability of the genome sequence has accelerated the biological study of *C. albicans* and marks the advent of the post-genome era. Moreover, new techniques, such as RNA-Seq, ChIP-chip, and proteomics were developed to generate valuable large-scale resources to systematically study the function of *C. albicans* genes.

Comparative Genome Sequence Analysis

In 2009, Butler et al. [5] reported the genome sequences of six species of the *Candida* clade and compared their genomic features associated with pathogenicity and sexual mating. The sequenced species are *C. albicans* (WO-1, White-Opaque switching-1, a clinical isolate with *MTL*α/α genotype), *Candida tropicalis*, *Candida parapsilosis*, *Lodderomyces elongisporu*, *Candida guilliermondii* and *Candida lusitaniae*. These species span a wide evolutionary range and differ in a variety of biological aspects including morphogenesis, pathogenesis and sexual reproduction [5]. Except for *Lodderomyces elongisporus,* the other five species are all pathogenic and often isolated from clinical sources. The genome sequence of *Candida dubliniensis*, a closely related species of *C. albicans*, has also been sequenced by Jackson et al. [6]. Comparative analysis of the genome sequences of these pathogenic and non-pathogenic species not only identifies a lot of new genes, but also a number of species-specific virulence factors. The pathogenic *Candida* species show significant expansion of several gene families including those encoding cell wall, secreted and transporter proteins [6]. For example, the Als adhesins, which are associated with virulence in *C. albicans*, are enriched in pathogenic species but not found in non-pathogenic species like *Saccharomyces cerevisiae*. Analysis of the structural features of mating-type loci and the components of the mating and meiosis pathways indicate that the *Candida* species may have unique and diverse mechanisms in the regulation of sexual reproduction. The association of white-opaque phenotypic switching and sexual mating in *C. albicans* and *C. tropicals* provides a good example [7-9].

Transcriptome Analysis

Thanks to the availability of genomic sequences, new techniques, such as microarray, tiling-array and RNA-Seq, have been developed to characterize the global transcriptional profiles of *Candida* species. During the past fifteen years, many studies of global gene expression analysis have been published to elucidate the underlying mechanisms of drug responses, phenotypic transitions, biofilm development and sexual mating. For instance, Bruno et al. [10] comprehensively annotated the transcriptome of *C. albicans* grown under several conditions by RNA-Seq analysis. They focused on differentially expressed genes involved in yeast-hyphal transition. In the same year, the Johnson lab tested the transcriptomes of two distinct heritable cell types, white and opaque, of *C. albicans* by RNA-Seq analysis [11]. The global expression profiles of the two cell types shed new insights into regulatory mechanisms of this unique phenotypic transition. These studies also identified a plenty of previously unknown non-coding RNAs and systemically characterized the 5' and 3'-terminal untranslated regions (UTRs) of differentially expressed genes under different conditions or in different development phases.

ChIP-chip and ChIP-Seq were recently applied to studying the roles of transcription factors in phenotypic transitions and biofilm formation in *C. albicans* [12,13]. The combination of RNA-Seq, ChIP-chip (and ChIP-Seq) and bioinformatics provides powerful tools and produces comprehensive data to understand global regulations of gene transcription and signal transduction networks in *C. albicans*. A master regulatory circuit has been defined by Noble et al. (2012) [13] by using these experimental techniques coupled with thorough bioinformatic analysis.

Proteomics Analysis

Proteomics analysis may provide vital information about the biology and pathogenic features of *C. albicans* since mRNA levels do not always correlate with protein levels [14]. The analysis of protein profiles in the fungus would more directly reveal the molecular regulatory mechanisms of pathogenicity and other biological aspects. The importance of this technique is becoming increasingly recognized.

Systematic Analysis of Gene Function

A couple of genetic features of *C. albicans* hindered the research of genetics and molecular biology in this species. First, *C. albicans* belongs to the CTG clade, in which the CTG codon is translated into serine instead of leucine. Second, despite *C. albicans* can mate under some laboratory conditions, it lacks a complete meiotic sexual cycle [15]. Recently, large-scale gene knockout and over expression systems in *C. albicans* have been developed [16]. These techniques provide excellent tools and resources to systematically study the function of genes. For instance, Noble et al. (2010) [17] recently deleted about 670 genes in *C. albicans* and found that the correlation between morphogenetic switching and pathogenicity is not as perfect as previously thought. For example, genes involved in the synthesis of glycolipid glucosylceramide, which are not required for filamentous development, play an important

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role in virulence. The Soll lab recently constructed an over-expression library of ~100 transcription factors involved in adhesion and biofilm formation in *C. albicans* [18]. The Mitchell lab and the Johnson lab also generated several sets of *C. albicans* mutants of transcription factors, cell wall proteins and kinases [19,20]. In addition, Chauvel and colleagues are making an over-expressing library of all *C. albicans* ORFs [21]. These resources will benefit the whole community of *Candida* research and accelerate the systematic exploration of gene functions in *C. albicans*.

The understanding of the molecular mechanisms of pathogenesis, morphogenesis and other aspects in *C. albicans* and related species will not only benefit the discovery of potential antifungal targets and the development of novel drugs, but also provide a model system for the study of other human fungal pathogens. The *Candida* research community is growing fast. The collaboration among laboratories with different backgrounds is becoming more important than ever to explore the biological complexity of *C. albicans*. The good thing is that many genomic and functional genomic analysis tools have been adapted to study the genomic features and the roles of *C. albicans* genes. These new techniques will make this pathogenic organism more tractable for the future study.

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