Chapter 4
Application of Systems Biology Approaches for Host-Fungal Interaction in Animals

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4.1 Introduction

Fungi are the major pathogens of plant, insects, and ectothermic vertebrates, but there are only a few of them that can cause diseases in mammals (Casadevall et al. 2019). Interaction between pathogens and their host can induce changes both in the host and in the pathogen, which might result in either the clearing of the pathogen from host or the establishing the pathogen within the host. These host-pathogen interactions can be analyzed with the help of systems biology approaches which generates novel hypothesis or decipher the effects of particular molecules or genes across the biological network (Peters et al. 2019).

Systems biology aims to understand the complex and dynamic biological information in the larger picture and requires the integration of different type of omics data such as proteomics, genomics, transcriptomics, and metabolomics (Pinu et al. 2019). This approach unravels the intricate network of interactions between host and fungal pathogen and helps to elucidate the complex pathogenesis processes of fungal interactions. Sayers et al. (2019) developed a web-based integrative resource for the analysis of virulence factor of different pathogens including fungus that causes infectious disease in human and animals. Virulence factors are small molecules that allow the microbial pathogens to survive and leads to diseased state in host.

To understand the infection mechanism, the whole host-fungal interaction system is more useful instead of investigating pathogen or host separately and is crucial to develop more effective solution. The combined investigation of host-fungal

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interaction might provide the understanding about the infectious disease in a way giving insight into the following questions.

1. How to identify direct interaction between fungus and host proteins during the infection and/or invasion process?
2. What signaling pathways and processes of the pathogen/host are implicated?
3. How to detect the crosstalk among the pathogen-host biochemical network?
4. What are the specific and unspecific responses of the host to pathogen invasion?
5. What specific protein or pathways could be targeted to control fungal infection and invasion in animals?

4.2 Systems Biology of Infection

Systems biology is an interdisciplinary research field which focuses on the study of nonlinear interactions among biological entities through combination of mathematical and computational approaches to study host-fungal interaction in biological system. This host-fungal interaction may be between proteins, nucleotides, metabolites, and small ligands. The traditional research typically focuses on single gene or fewer genes. The systems biology approach is insightful to understand physiology and infectious disease at cellular and molecular, network level. Systems biology approaches are categorized into bottom-up and top-down, where the bottom-up focus on network reconstruction through mathematical models while top-down approaches involves metabolic network reconstruction using "omics" data generated through high-throughput genomic techniques using appropriate statistical and bioinformatics methodologies (Shahzad and Loor 2012).

4.3 Data in Systems Biology and Analysis

Understanding the complex host fungal interaction requires high-throughput data as well as the annotations information available from public repositories (Table 4.1).

4.3.1 Omics-Based Data

Fungal omics such as genomics, transcriptomics, proteomics, and metabolomics help to understand basic fungal biology and its associated functional implications. Due to recent advancement in sequencing techniques as well as a small size of the fungal genome, the analysis of the fungal genome and proteome data becomes much easier. The information obtained from omics data analysis may enhance our

Table 4.1 Web-based bioinformatics resources for fungal systems biology

Resources	Description	Website
AsperCyc	*Aspergillus* metabolic pathways	www.aspercyc.org
Aspergillus genome DB (AspGD)	AspGD is an organized collection of genetic and molecular biological information about the filamentous fungi of the genus *Aspergillus*	www.aspgd.org
Comparative fungal genomics platform (CFGP)	CFGP was designed for comparative genomics projects with diverse fungal genomes	http://cfgp.riceblast.snu.ac.kr
Candida genome DB (CGD)	A resource for genomic sequence data and gene and protein information for ***Candida*** *albicans* and related species	www.candidagenome.org
Ensembl Fungi	It is browser for fungal genomes	http://fungi.ensembl.org
FindFungi	Sequence classification pipeline to identify fungal sequences in public metagenome datasets	http://bioinformatics.czc.hokudai.ac.jp/findfungi/
FunCatDB	Gene-annotations	
Fungal databases	U.S. National Fungus Collections, ARS, USDA	https://nt.ars-grin.gov/fungaldatabases/
FungiDB	It is an integrated genomic and functional genomic database for the fungi	www.fungidb.org
FungiFun	FungiFun is a user-friendly web tool for functional enrichment analysis of fungal genes and proteins	https://sbi.hki-jena.de/fungifun/fungifun.php
Omnifung	Data warehouse for omics data	www.omnifung.hki-jena.de
PhiBase	Database of virulence genes	www.phibase.org
Proteopathogen	Protein database for studying *Candida albicans*-host interaction	http://proteopathogen.dacya.ucm.es
UNITE	Web-based database and sequence management environment for the molecular identification of fungi	https://unite.ut.ee/

understanding about pathophysiology of infectious process and their underlying mechanisms of complex fungal biological process such as host-fungal interactions.

The free open source software "Bioconductor (Version 3.11)" provides 1904 software package, 961 annotation, and 392 experimental datasets for bioinformatics analysis and comprehension of high-throughput genomic data.

4.3.1.1 Genomics

The new sequencing technology generates huge genomics datasets at a low cost and in a short time. This enables to explore more genomic information of fungal pathogen and would help to improve the diagnostic methods. SNP identification is one of the important methods for characterization of variants of different pathogens

as well as to study the susceptibility of humans for different infections or pathogens. *Saccharomyces cerevisiae* is the first fungus whose complete genome sequence was available in 1996 (Goffeau et al. 1996); since then a number of human pathogen fungal genome have been published. The genome of *C. albicans* was published in 2004 (Jones et al. 2004), and the genome of *C. neoformans* and *A. fumigatus* were published in 2005 (Loftus et al. 2005; Nierman et al. 2005). There are also many freely sources available for different pathogenic fungal species (Table 4.1) such as Aspergillus Genome Database (AspGD) (Cerqueira et al. 2014) and Central Aspergillus Data Repository (CADRE) (Mabey et al. 2004) for *Aspergillus* and Candida Genome Database (CGD) (Skrzypek et al. 2017) and CandidaDB (d'Enfert et al. 2005) for *Candida* species. This freely available information allows researchers to identify and to investigate more about the host fungal interactions.

4.3.1.2 Transcriptomics

Pathogenic fungus during the course of infection process needs to effectively adapt to the host environment. These adaptation mechanisms are controlled by various transcriptional changes and it provides critical information regarding fungal pathogenesis (Amorim-Vaz and Sanglard 2015). The comparative analysis of the host and the fungal pathogen might help to design new antifungal drugs and to explore the clustered genes involved in the process of pathogenicity (Meijueiro et al. 2014).

Microarray, RNA-Seq, and nanoString are powerful tools to study the interaction between fungal pathogen and their host during the infection. *Cryptococcus neoformans* and *Aspergillus fumigatus* are the two important fungal species that cause high mortality in immune-compromised patients (Brown et al. 2012), and their transcriptomics study has already been performed (Chen et al. 2014; McDonagh et al. 2008). Bruno et al. in 2010 (Bruno et al. 2010) used RNA sequencing to generate a high-resolution transcriptome map of human pathogen *Candida albicans* under different environmental conditions and identified 602 new transcriptionally active regions (TARs).

Deep sequencing also has been used to identify novel functional small RNAs, which has a great implication in the regulation of global gene expression in human pathogenic fungus (Nicolas and Ruiz-Vazquez 2013). Arthanari et al. (2014) used RNA sequencing data from ABI SOLiD platform to identify 939 novel long noncoding RNA (IncRNA) and 477 new natural antisense transcripts (NAT) from ascomycete fungus *Neurospora crassa* under different light and temperature conditions. Gene Expression Omnibus (GEO) (Barrett et al. 2013; Edgar et al. 2002) and ArrayExpress (Rustici et al. 2013) are the freely publicly available databases of fungal transcriptomics data.

Some reported virulence factors have been found to be related to transcriptional reprogramming associated with phase transition from avirulent mycelia to pathogenic yeast. For instance, in case of *Paracoccidioides* spp., which causes paracoccidioidomycosis, the transition between these forms has been an important

virulence factor (Tavares et al. 2015). *Candida albicans*, responsible for candidiasis, under comprised immunity and other opportunistic conditions results in superficial mucosal colonization and establishment of the systemic infection (Cheng et al. 2013; Wartenberg et al. 2014). According to RNA-seq studies in mice, during the vaginal infections caused by *C. albicans,* overexpression of aspartyl-proteinases 4, 5, and 6 (SAP4–6) has been reported which are hypha-associated secreted enzymes and function as inflammasome activators (Bruno et al. 2015). The virulence factor for *Cryptococcus* is a transcription factor Rim101 that is involved in the cell wall composition regulation (O'Meara et al. 2013). Cell wall forms a barrier at host-pathogen interface and is part of immune system. The structural integrity of the cell wall is maintained by the cell wall integrity signaling pathway that involves various crucial kinases. Dual RNA-seq is a high-throughput sequencing for simultaneous transcriptomic analysis of pathogen and host to explore the regulatory networks during the fungal infection (Das et al. 2015; Rienksma et al. 2015; Westermann et al. 2012).

4.3.1.3 Proteomics

Proteomics is another tool for the examination of expression patterns in the biological system. Proteins are the functional determinants and might have various roles such as to build the cellular structure; to mediate signal transduction, involved in the gene regulation; to influence different cellular processes; or to function as enzyme. Proteomic studies were initially performed using 2D-PAGE followed by mass spectrometry. Mass spectrometry is still the gold standard for proteomic analysis in the field of systems biology.

The release of the genome sequences of *Candida albicans* (Braun et al. 2005; Jones et al. 2004) and *Aspergillus fumigatus* (Nierman et al. 2005) has been of great benefit for a more detailed insight into the evolution and pathogenesis of these medically important fungus since for these pathogenic fungus, 2D gel proteome reference maps are available (Kniemeyer et al. 2011). Vodisch et al. (2009) identified 334 different mycelial proteins via 2D gel electrophoresis of *Aspergillus fumigatus.*

4.3.2 Image-Based Data

Image-based systems biology approaches are important tools for the investigation and elucidation of pathobiology of fungal infection. It can be divided into four basic steps: (i) extraction of image data through experimental techniques, (ii) preprocessing of the data, (iii) quantitative characterization of biological processes, and (iv) and image-based model development (Fig. 4.1).

Multiphoton microscopy (MPM) and fluorescence microscopy is one of the most valuable tools for live-cell imaging in infection research (Ettinger and Wittmann 2014; Sun et al. 2017). For the analysis of host-pathogen interaction, a large number

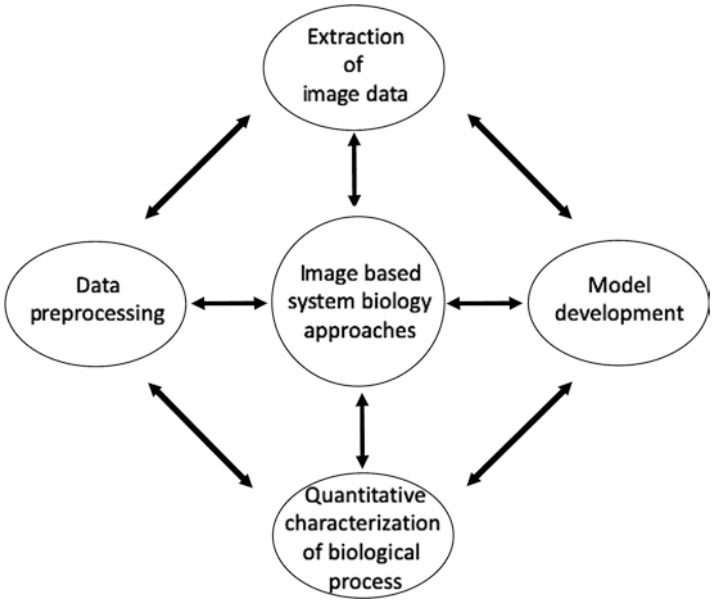

Fig. 4.1 Diagrammatic representation of image-based systems biology approaches

of images are required that can be obtained by different experimental approaches such as fluorescence microscopy and positron emission tomography-computed tomography (PET/CT). Ibrahim-Granet et al. (2003) described the detail analysis of interaction between *A. fumigatus* and phagocytes using fluorescence microscopy and manual image analysis.

Manual image data analysis with regard to host-pathogen interaction is time consuming, and also error-prone; on the other hand, an automated image data analysis can analyze a large amount of data in a shorter period of time and is not labor extensive. Mech et al. (2011) developed an automated image analysis for the host-pathogen interaction between *Aspergillus fumigatus* conidia with immune cells. They used confocal laser scanning microscopy images from macrophages with different *A. fumigatus* strains. In this study, phagocytosed cells were differentially stained with fluorescent dyes and visualized with confocal laser scanning microscope, leading to discrimination between macrophages, internalized conidia, and non-internalized conidia. Currently there are a number of image analysis tools available for fungal analysis (Brunk et al. 2018; Cairns et al. 2019; Mader et al. 2015; Wurster et al. 2019). All image analysis methods comprise mainly three main parts: (i) preprocessing, (ii) segmentation, and (iii) classification.

Image-based systems biology is a relatively new scientific approach that comprises imaging, quantitative characterization, and modeling. In host-fungal interactions, image-derived models have been used to investigate the phagocytosis of fungal spores and the growth of fungal hyphae (Mech et al. 2011). It enhances our understanding of many aspects of cell migration and interaction behavior of the

immune cells. Image-based systems biology focuses on the spatial factors and on cellular morphology (Horn et al. 2012).

4.4 Modeling

The computational modeling of networks of the genes, transcripts, proteins, and metabolites is of great importance in biomedical research to understand the molecular mechanism of the host-fungal interactions and helps to understand the complex regulatory mechanism. The aim of the modeling is to support the standardized design of experiments, to generate the hypothesis, and to validate the hypothesis. The modeling also allows the prediction of novel regulatory biological strategies (Horn et al. 2012). May and Anderson (1979) described the host-pathogen interaction through the evolutionary model. Due to the challenges of modeling of a complex system, only a few models of fungal-human interactome network have been studied (Horn et al. 2012). Rodrigues et al. (2018) developed transkingdom network (TransNet) analysis pipeline that allows to make biological inferences. They constructed a network using correlation between differentially expressed elements and integration of high-throughput data from different taxonomic kingdoms.

4.4.1 Network Modeling

Biological network modeling enables to study how the system can respond to the ever-changing external environment. Predictive power of such model enables the diagnosis by the prediction of biomarkers and drug targets. Cellular behavior of organism can be represented by gene regulatory network, protein-protein network, signaling network, and metabolic network. In the network modeling, the nodes represent molecular entities such as genes, proteins, and metabolites, and the edges represent the relationship between the nodes and can be modeled in different ways like directed or undirected edges (Horn et al. 2012). Aho et al. (2010) made an effort to reconstruct a model, which integrated the genomics, transcriptomics, proteomics, and metabolic data. Some of the biological networks of fungus that have been extensively studied in recent years have been discussed below.

4.4.1.1 Gene Regulatory Network

Gene regulatory network (GRN) is the network of genes that either interact physically or have genetic interaction to regulate a pathway or to carry out a specific role (Karlebach and Shamir 2008). Gene regulatory network helps to predict the gene that might function as central and key player in the network. It also describes the

relationship between the regulatory components and can help to predict their target gene (Guo et al. 2016). Among the fungal species, GRN studies has been extensively focused on *Saccharomyces cerevisiae* (Darabos et al. 2011; Guelzim et al. 2002; Hu et al. 2007; Kim et al. 2006; Lee et al. 2002; Pe'er et al. 2002; Segal et al. 2003), *Candida albicans* (Homann et al. 2009; Ramachandra et al. 2014), and *Fusarium graminearum* (Guo et al. 2016). Many computational methods such as Gaussian graphical model (Kishino and Waddell 2000; Schafer and Strimmer 2005), probabilistic Boolean network (Glass and Kauffman 1973; Kauffman 1969; Shmulevich et al. 2002), linear model, and regression and Bayesian network (Friedman et al. 2000; Pe'er et al. 2002; Segal et al. 2003) are available for GRN reconstruction. Pe'er et al. (2002) used Bayesian network to reconstruct yeast GRN. Tierney et al. (2012) generated the first interspecies computational model of host-pathogen interactions and used it to decipher the mechanism of microbial pathogenesis. They used RNA-Seq expression data from *Candida albicans* and bone marrow-derived dendritic cells from *M. musculus*.

4.4.1.2 Protein-Protein Interaction (PPI) Network

In the post-genomic era, genes and its corresponding proteins are very useful for the identification of intra- and interspecies protein interaction networks (Durmus et al. 2015). These protein-protein interaction (PPI) networks have been used to identify the host immune-associated genes and the pathogenic effector proteins associated with host infection. Wang et al. (2013) integrated multiple omics data and based on the inference of ortholog-based PPI and dynamic modeling of regulatory responses have constructed an interspecies PPI network for *Candida albicans* and zebrafish. Development of experimental techniques to produce large-scale molecular interaction data and further an increase in the amount of experimentally validated host-fungal PPI data provides opportunity to perform a number of computational studies to investigate infection mechanism for different pathogen types (Durmus et al. 2015).

4.4.1.3 Signaling Network

Signaling network is a cell-to-cell communication network that allows the cell to respond to external signals through the change in transcription. When the cell receives the external signal through its membrane, it activates the cascade of events and ultimately affects the transcriptional. These signals or stimulus can be of different type such as chemical, physical, radiation, pathogen, etc. An excellent example of a highly conserved signaling network within all eukaryotes is the Regulation of Ace2 and Morphogenesis (RAM) network (Kurischko et al. 2005; Nelson et al. 2003; Saputo et al. 2012). This network is most extensively studied in *Saccharomyces cerevisiae* and *Candida albicans* and is less characterized for pathogenic fungus.

4.4.1.4 Metabolic Network

During infection, the pathogen interacts with the host cell and it causes alterations in the level of metabolites by affecting the host metabolic pathways (Cakir et al. 2020). Metabolic network model describes the metabolic state of the cell, and it allows for an in-depth insight into the molecular mechanisms and systems level predictions of metabolism in a variety of organisms. Recently, Wang et al. (2018) used a systems biology approach to predict and characterize human gut microbial metabolite in colorectal cancer.

The first genome-scale metabolic model for *Saccharomyces cerevisiae* was presented in 2003 (Forster et al. 2003), and it was the first and the most studied genome-scale network reconstruction for the eukaryotic organism. Since eukaryotic organisms are very complex in nature, researchers are continuing applying their efforts to improve and upgrade information into the metabolic network. Till date a number of genome-scale reconstruction of metabolic networks have been released (Dobson et al. 2010; Duarte et al. 2004; Heavner et al. 2012; Herrgard et al. 2008; Mo et al. 2009; Nookaew et al. 2008; Osterlund et al. 2013; Zomorrodi and Maranas 2010). *Saccharomyces cerevisiae* metabolic network has also been used as the basis for construction of metabolic models for other yeast, such as *Saccharomyces pombe* (Sohn et al. 2012), *Yarrowia lipolytica* (Loira et al. 2012), *Pichia pastoris,* and *Pichia stipites* (Caspeta et al. 2012). There are many researchers who are working on the tool development for reconstruction of genome-scale metabolic network (O'Brien et al. 2015; Pusa et al. 2020; Tefagh and Boyd 2020). Recently, Tefagh and Boyd in 2020 (Tefagh and Boyd 2020) proposed SWIFTCC and SWIFTCORE as effective methods for flux consistency checking and for the context specific reconstruction of genome-scale metabolic networks, while Pusa et al. (2020) developed a mathematical tool "MOOMIN" which uses genome-scale metabolic reconstruction to infer metabolic changes from differential expression data.

4.5 Conclusion and Future Implications

Unlike bacterial and viral infections, the fungal infections are uncommon and have been mainly associated with the immunocompromised patients due to conditions such as transplantation, tuberculosis, and HIV due to which they lead to a high mortality rate (Kumar and Ruhel 2019; Romani 2011). Understanding the intrinsic complexity of the invasive infection and exploring the transcriptional reprogramming in the host cells upon fungal infection might help to design more efficient and broad-range therapeutic strategies and drug targets. This would also expand the knowledge about the biomarkers for progression of the infection. Noncoding RNAs (ncRNAs) are emerging as important players in various stages of infection process such as colonization of cells and signaling and in other pathologically related functions. It would be interesting to explore the involvement of more players such as the noncoding RNAs along with the epigenetic factors during the host-fungal

interaction and its implications on the infection process. The study of ncRNAs by small RNA (sRNA) sequencing during the fungal infection in the host cells combined with transcriptomics data could be another approach.

The recent advanced high-throughput techniques such as RNA-seq, sRNA-seq, and dual-seq analysis have been of a great importance to understand the crosstalk between various pathways triggered by the fungus pathogen in the infected host cells. Expansion in the data repositories related to host-fungal interaction along with systems biology modeling could be helpful for personalized medicine which is an emerging research (Dix et al. 2016). Combining various approaches will be an important route for infection-related research over the next decade (Yeung et al. 2019). Integration of the experimental data, computational and mathematical model, and information from the database provide a better model (Fig. 4.2) which can be used to validate a working hypothesis as well as to test new computational models. In future, the modeling of host-fungal interaction networks will be important to

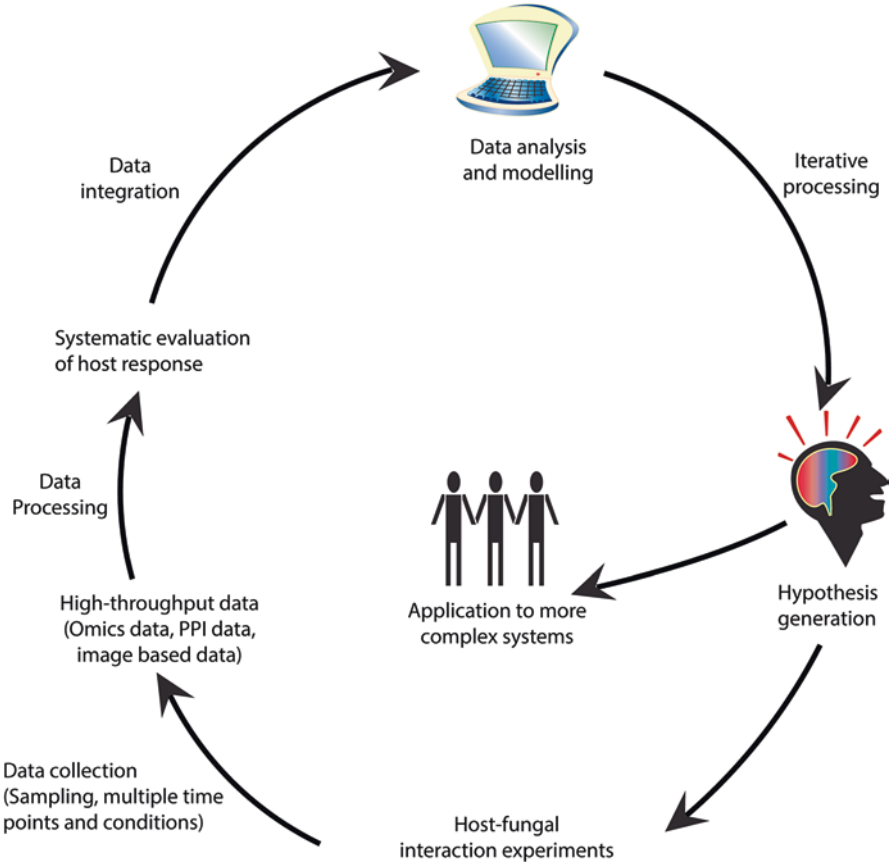

Fig. 4.2 An illustration of the various system approaches that can be applied to test the hypothesis to study host-fungal interactions

complement the experimental work to enhance the understanding of the system, to reduce animal experiments, and to generate and test hypothesis faster.

References

Aho T et al (2010) Reconstruction and validation of RefRec: a global model for the yeast molecular interaction network. PLoS One 5(5):e10662

Amorim-Vaz S, Sanglard D (2015) Novel approaches for fungal transcriptomics from host samples. Front Microbiol 6:1571

Arthanari Y et al (2014) Natural antisense transcripts and long non-coding RNA in Neurospora crassa. PLoS One 9(3):e91353

Barrett T et al (2013) NCBI GEO: archive for functional genomics data sets--update. Nucleic Acids Res 41(Database issue):D991–D995

Braun BR et al (2005) A human-curated annotation of the Candida albicans genome. PLoS Genet 1(1):36–57

Brown GD et al (2012) Hidden killers: human fungal infections. Sci Transl Med 4(165):165rv113

Brunk M et al (2018) HyphaTracker: an ImageJ toolbox for time-resolved analysis of spore germination in filamentous fungi. Sci Rep 8(1):605

Bruno VM et al (2010) Comprehensive annotation of the transcriptome of the human fungal pathogen Candida albicans using RNA-seq. Genome Res 20(10):1451–1458

Bruno VM et al (2015) Transcriptomic analysis of vulvovaginal candidiasis identifies a role for the NLRP3 inflammasome. MBio 6(2):e00182–e00115

Cairns TC et al (2019) A quantitative image analysis pipeline for the characterization of filamentous fungal morphologies as a tool to uncover targets for morphology engineering: a case study using aplD in Aspergillus niger. Biotechnol Biofuels 12:149

Cakir T et al (2020) Novel approaches for systems biology of metabolism-oriented pathogen-human interactions: a mini-review. Front Cell Infect Microbiol 10:52

Casadevall A et al (2019) The 'amoeboid predator-fungal animal virulence' hypothesis. J Fungi (Basel) 5(1):10

Caspeta L et al (2012) Genome-scale metabolic reconstructions of Pichia stipitis and Pichia pastoris and in silico evaluation of their potentials. BMC Syst Biol 6:24

Cerqueira GC et al (2014) The Aspergillus genome database: multispecies curation and incorporation of RNA-Seq data to improve structural gene annotations. Nucleic Acids Res 42(Database issue):D705–D710

Chen Y et al (2014) The Cryptococcus neoformans transcriptome at the site of human meningitis. MBio 5(1):e01087–e01013

Cheng S et al (2013) Profiling of Candida albicans gene expression during intra-abdominal candidiasis identifies biologic processes involved in pathogenesis. J Infect Dis 208(9):1529–1537

d'Enfert C et al (2005) CandidaDB: a genome database for Candida albicans pathogenomics. Nucleic Acids Res 33(Database issue):D353–D357

Darabos C et al (2011) Additive functions in boolean models of gene regulatory network modules. PLoS One 6(11):e25110

Das A et al (2015) Dual RNA sequencing reveals the expression of unique transcriptomic signatures in lipopolysaccharide-induced BV-2 microglial cells. PLoS One 10(3):e0121117

Dix A et al (2016) Use of systems biology to decipher host-pathogen interaction networks and predict biomarkers. Clin Microbiol Infect 22(7):600–606

Dobson PD et al (2010) Further developments towards a genome-scale metabolic model of yeast. BMC Syst Biol 4:145

Duarte NC, Herrgard MJ, Palsson BO (2004) Reconstruction and validation of Saccharomyces cerevisiae iND750, a fully compartmentalized genome-scale metabolic model. Genome Res 14(7):1298–1309

Durmus S et al (2015) A review on computational systems biology of pathogen-host interactions. Front Microbiol 6:235

Edgar R, Domrachev M, Lash AE (2002) Gene expression omnibus: NCBI gene expression and hybridization array data repository. Nucleic Acids Res 30(1):207–210

Ettinger A, Wittmann T (2014) Fluorescence live cell imaging. Methods Cell Biol 123:77–94

Forster J et al (2003) Genome-scale reconstruction of the Saccharomyces cerevisiae metabolic network. Genome Res 13(2):244–253

Friedman N et al (2000) Using Bayesian networks to analyze expression data. J Comput Biol 7(3–4):601–620

Glass L, Kauffman SA (1973) The logical analysis of continuous, non-linear biochemical control networks. J Theor Biol 39(1):103–129

Goffeau A et al (1996) Life with 6000 genes. Science 274(5287):546, 563–547

Guelzim N et al (2002) Topological and causal structure of the yeast transcriptional regulatory network. Nat Genet 31(1):60–63

Guo L et al (2016) Compartmentalized gene regulatory network of the pathogenic fungus Fusarium graminearum. New Phytol 211(2):527–541

Heavner BD et al (2012) Yeast 5 – an expanded reconstruction of the Saccharomyces cerevisiae metabolic network. BMC Syst Biol 6:55

Herrgard MJ et al (2008) A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. Nat Biotechnol 26(10):1155–1160

Homann OR et al (2009) A phenotypic profile of the Candida albicans regulatory network. PLoS Genet 5(12):e1000783

Horn F et al (2012) Systems biology of fungal infection. Front Microbiol 3:108

Hu Z, Killion PJ, Iyer VR (2007) Genetic reconstruction of a functional transcriptional regulatory network. Nat Genet 39(5):683–687

Ibrahim-Granet O et al (2003) Phagocytosis and intracellular fate of Aspergillus fumigatus conidia in alveolar macrophages. Infect Immun 71(2):891–903

Jones T et al (2004) The diploid genome sequence of Candida albicans. Proc Natl Acad Sci U S A 101(19):7329–7334

Karlebach G, Shamir R (2008) Modelling and analysis of gene regulatory networks. Nat Rev Mol Cell Biol 9(10):770–780

Kauffman SA (1969) Metabolic stability and epigenesis in randomly constructed genetic nets. J Theor Biol 22(3):437–467

Kim H, Hu W, Kluger Y (2006) Unraveling condition specific gene transcriptional regulatory networks in Saccharomyces cerevisiae. BMC Bioinformatics 7:165

Kishino H, Waddell PJ (2000) Correspondence analysis of genes and tissue types and finding genetic links from microarray data. Genome Inform Ser Workshop Genome Inform 11:83–95

Kniemeyer O et al (2011) Identification of virulence determinants of the human pathogenic fungi Aspergillus fumigatus and Candida albicans by proteomics. Int J Med Microbiol 301(5):368–377

Kumar R, Ruhel R (2019) Emergence of invasive fungal infection: diagnosis and treatment in humans. In: Gupta A, Singh N (eds) Recent developments in fungal diseases of laboratory animals. Fungal biology. Springer, Cham, pp 131–148

Kurischko C et al (2005) A role for the Saccharomyces cerevisiae regulation of Ace2 and polarized morphogenesis signaling network in cell integrity. Genetics 171(2):443–455

Lee TI et al (2002) Transcriptional regulatory networks in Saccharomyces cerevisiae. Science 298(5594):799–804

Loftus BJ et al (2005) The genome of the basidiomycetous yeast and human pathogen Cryptococcus neoformans. Science 307(5713):1321–1324

Loira N et al (2012) A genome-scale metabolic model of the lipid-accumulating yeast Yarrowia lipolytica. BMC Syst Biol 6:35
Mabey JE et al (2004) CADRE: the Central Aspergillus Data REpository. Nucleic Acids Res 32(Database issue):D401–D405
Mader U et al (2015) Image-processing scheme to detect superficial fungal infections of the skin. Comput Math Methods Med 2015:851014
May RM, Anderson RM (1979) Population biology of infectious diseases: part II. Nature 280(5722):455–461
McDonagh A et al (2008) Sub-telomere directed gene expression during initiation of invasive aspergillosis. PLoS Pathog 4(9):e1000154
Mech F et al (2011) Automated image analysis of the host-pathogen interaction between phagocytes and Aspergillus fumigatus. PLoS One 6(5):e19591
Meijueiro ML et al (2014) Transcriptome characteristics of filamentous fungi deduced using high-throughput analytical technologies. Brief Funct Genomics 13(6):440–450
Mo ML, Palsson BO, Herrgard MJ (2009) Connecting extracellular metabolomic measurements to intracellular flux states in yeast. BMC Syst Biol 3:37
Nelson B et al (2003) RAM: a conserved signaling network that regulates Ace2p transcriptional activity and polarized morphogenesis. Mol Biol Cell 14(9):3782–3803
Nicolas FE, Ruiz-Vazquez RM (2013) Functional diversity of RNAi-associated sRNAs in fungi. Int J Mol Sci 14(8):15348–15360
Nierman WC et al (2005) Genomic sequence of the pathogenic and allergenic filamentous fungus Aspergillus fumigatus. Nature 438(7071):1151–1156
Nookaew I et al (2008) The genome-scale metabolic model iIN800 of Saccharomyces cerevisiae and its validation: a scaffold to query lipid metabolism. BMC Syst Biol 2:71
O'Brien EJ, Monk JM, Palsson BO (2015) Using genome-scale models to predict biological capabilities. Cell 161(5):971–987
O'Meara TR et al (2013) Cryptococcus neoformans Rim101 is associated with cell wall remodeling and evasion of the host immune responses. MBio 4(1):e00522–e00512
Osterlund T et al (2013) Mapping condition-dependent regulation of metabolism in yeast through genome-scale modeling. BMC Syst Biol 7:36
Pe'er D, Regev A, Tanay A (2002) Minreg: inferring an active regulator set. Bioinformatics 18(Suppl 1):S258–S267
Peters JM, Solomon SL, Itoh CY, Bryson BD (2019) Uncovering complex molecular networks in host–pathogen interactions using systems biology. Emerg Top Life Sci 3(4):371–378
Pinu FR et al (2019) Systems biology and multi-omics integration: viewpoints from the metabolomics research community. Metabolites 9(4):76
Pusa T et al (2020) MOOMIN – Mathematical explOration of 'Omics data on a MetabolIc Network. Bioinformatics 36(2):514–523
Ramachandra S et al (2014) Regulatory networks controlling nitrogen sensing and uptake in Candida albicans. PLoS One 9(3):e92734
Rienksma RA et al (2015) Comprehensive insights into transcriptional adaptation of intracellular mycobacteria by microbe-enriched dual RNA sequencing. BMC Genomics 16:34
Rodrigues RR, Shulzhenko N, Morgun A (2018) Transkingdom networks: a systems biology approach to identify causal members of host-microbiota interactions. Methods Mol Biol 1849:227–242
Romani L (2011) Immunity to fungal infections. Nat Rev Immunol 11(4):275–288
Rustici G et al (2013) ArrayExpress update--trends in database growth and links to data analysis tools. Nucleic Acids Res 41(Database issue):D987–D990
Saputo S et al (2012) The RAM network in pathogenic fungi. Eukaryot Cell 11(6):708–717
Sayers S et al (2019) Victors: a web-based knowledge base of virulence factors in human and animal pathogens. Nucleic Acids Res 47(D1):D693–D700
Schafer J, Strimmer K (2005) An empirical Bayes approach to inferring large-scale gene association networks. Bioinformatics 21(6):754–764

Segal E et al (2003) Module networks: identifying regulatory modules and their condition-specific regulators from gene expression data. Nat Genet 34(2):166–176
Shahzad K, Loor JJ (2012) Application of top-down and bottom-up systems approaches in ruminant physiology and metabolism. Curr Genomics 13(5):379–394
Shmulevich I et al (2002) Probabilistic Boolean networks: a rule-based uncertainty model for gene regulatory networks. Bioinformatics 18(2):261–274
Skrzypek MS et al (2017) The Candida genome database (CGD): incorporation of assembly 22, systematic identifiers and visualization of high throughput sequencing data. Nucleic Acids Res 45(D1):D592–D596
Sohn SB et al (2012) Genome-scale metabolic model of the fission yeast Schizosaccharomyces pombe and the reconciliation of in silico/in vivo mutant growth. BMC Syst Biol 6:49
Sun TY, Haberman AM, Greco V (2017) Preclinical advances with multiphoton microscopy in live imaging of skin cancers. J Invest Dermatol 137(2):282–287
Tavares AH et al (2015) Transcriptomic reprogramming of genus Paracoccidioides in dimorphism and host niches. Fungal Genet Biol 81:98–109
Tefagh M, Boyd SP (2020) SWIFTCORE: a tool for the context-specific reconstruction of genome-scale metabolic networks. BMC Bioinformatics 21(1):140
Tierney L et al (2012) An interspecies regulatory network inferred from simultaneous RNA-seq of Candida albicans invading innate immune cells. Front Microbiol 3:85
Vodisch M et al (2009) Two-dimensional proteome reference maps for the human pathogenic filamentous fungus Aspergillus fumigatus. Proteomics 9(5):1407–1415
Wang YC et al (2013) Interspecies protein-protein interaction network construction for characterization of host-pathogen interactions: a Candida albicans-zebrafish interaction study. BMC Syst Biol 7:79
Wang Q, Li L, Xu R (2018) A systems biology approach to predict and characterize human gut microbial metabolites in colorectal cancer. Sci Rep 8:6225
Wartenberg A et al (2014) Microevolution of Candida albicans in macrophages restores filamentation in a nonfilamentous mutant. PLoS Genet 10(12):e1004824
Westermann AJ, Gorski SA, Vogel J (2012) Dual RNA-seq of pathogen and host. Nat Rev Microbiol 10(9):618–630
Wurster S et al (2019) Live monitoring and analysis of fungal growth, viability, and mycelial morphology using the IncuCyte NeuroTrack processing module. MBio 10(3):e00673–e00619
Yeung A et al (2019) Using a systems biology approach to study host-pathogen interactions. Microbiol Spectr 7(2)
Zomorrodi AR, Maranas CD (2010) Improving the iMM904 S. cerevisiae metabolic model using essentiality and synthetic lethality data. BMC Syst Biol 4:178