FUNGAL BIOLOGY REVIEWS XXX (2018) 1–16

British Mycological Society promoting fungal science

journal homepage: www.elsevier.com/locate/fbr

Review

Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development

Zheng WANG[a,b], *Aditya GUDIBANDA*[a], *Ugochukwu UGWUOWO*[a], *Frances TRAIL*[c,d], *Jeffrey P. TOWNSEND*[a,b,e,*]

[a]*Department of Biostatistics, Yale University, New Haven, CT 06510, USA*
[b]*Department of Ecology and Evolutionary Biology, Yale University, New Haven, CT 06520, USA*
[c]*Department of Plant Biology, Michigan State University, East Lansing, MI 48824, USA*
[d]*Department of Plant, Soil and Microbial Sciences, Michigan State University, East Lansing, MI 48824, USA*
[e]*Program in Computational Biology and Bioinformatics, Yale University, New Haven, CT 06511, USA*

ARTICLE INFO

Article history:
Received 15 October 2017
Received in revised form
7 December 2017
Accepted 12 February 2018

Keywords:
Development
Evolution
Fungi
Genomics
Systems biology
Transcriptomics

ABSTRACT

Fungal model species have contributed to many aspects of modern biology, from biochemistry and cell biology to molecular genetics. Nevertheless, only a few genes associated with morphological development in fungi have been functionally characterized in terms of their genetic or molecular interactions. Evolutionary developmental biology in fungi faces challenges from a lack of fossil records and unresolved species phylogeny, to homoplasy associated with simple morphology. Traditionally, reductive approaches use genetic screens to reveal phenotypes from a large number of mutants; the efficiency of these approaches relies on profound prior knowledge of the genetics and biology of the designated development trait—knowledge which is often not available for even well-studied fungal model species. Reductive approaches become less efficient for the study of developmental traits that are regulated quantitatively by more than one gene via networks. Recent advances in genome-wide analysis performed in representative multicellular fungal models and non-models have greatly improved upon the traditional reductive approaches in fungal evo-devo research by providing clues for focused knockout strategies. In particular, genome-wide gene expression data across developmental processes of interest in multiple species can expedite the advancement of integrative synthetic and systems biology strategies to reveal regulatory networks underlying fungal development.

* *Corresponding author*. Department of Biostatistics, New Haven 06510, USA.
E-mail address: Jeffrey.Townsend@yale.edu (J. P. Townsend).

https://doi.org/10.1016/j.fbr.2018.02.001
1749-4613/

1. Introduction

"Morphology was studied because it was the material believed to be the most favorable for the elucidation of the problems of evolution…" (Bateson, 1922)

Developmental biology, one of the most longstanding and deeply examined subdisciplines in biology, reveals how complex life forms are constructed by the growth, repositioning, structure, and identity of cells and tissues. Examination of morphological development has been vigorous in almost every major organismal group, and knowledge of developmental biology has accumulated along with advances in cell biology, developmental genetics, and the systems biology. Nevertheless, we remain ignorant of some of the basic elements of how a body shape is planned and formed in response to genetic and environmental signals—even in well studied models.

Evolutionary biology and developmental biology have long been considered complementary disciplines, and their synthesis has recently been boosted by their merger into the exciting field of evolutionary developmental biology (a.k.a. Evo-Devo)—research that investigates the developmental processes and the evolution of those processes among different organisms (Hall, 2012). Among the oldest models in cell biology, fungi have contributed significantly to evolutionary developmental biology and in recent times continue to serve as highly tractable workhorses for genetics and genomics, and now systems biology revolution (Bennett and Arnold, 2001).

Fungal diversity and fungal development

Fungi represent one of the most diverse organismal groups on earth in terms of their ecology, their ubiquity, and their manifold morphological forms. Among eukaryotes, fungi are relatively simple in terms of their cell and tissue types, along with high genome diversity accompanying their wide ecological distribution (Alexopoulos, 2007; Blackwell, 2011; Mohanta and Bae, 2015; Stajich *et al.*, 2009; Taylor *et al.*, 2017; Zeng *et al.*, 2017). Fungal development encompasses a very wide range of complexity, ranging from unicellular yeasts that can be found in flowers and guts of beetles and wasps (Lachance *et al.*, 2013; Stefanini *et al.*, 2012), to the largest known fruiting body of a wood decaying fungus—weighing nearly 500 kg (Dai and Cui, 2011), to postfire fungi that blossom quickly and transiently after forest fires (Glassman *et al.*, 2016), to the oldest known mycelium—over 1500 years in age and 15 ha in occupied area (Smith *et al.*, 1992). In addition, morphological divergence, which in fungi commonly includes the evolution of morphologies of highly reduced complexity, can make it challenging to identify orthologous structures among even closely related lineages (Wang *et al.*, 2016). Many higher fungi produce elaborate sexual reproductive structures predominantly for survival during their sexual life cycles, but during their asexual cycle these same fungi produce simple but vigorous structures that generate myriad, short lived asexual spores for rapid dispersal. Convergent and divergent evolution of phenotypes are not rare in fungi (Alexopoulos, 2007; Nagy *et al.*, 2014; Shang *et al.*, 2016; Torruella *et al.*, 2015), often resulting from diverse ecological pressures on a limited set of available simple reduced morphologies. For example, many leaf endophytic fungi produce dark-colored, covered, small fruiting bodies, while their saprotrophic relatives produce bright-colored, exposed, large fruiting bodies (Ruibal *et al.*, 2008; Wang *et al.*, 2009). Like plants and animals, some fungi—despite their more limited palette of cell and tissue types—have evolved structures for specific functions that are not common to other fungi. Remarkable examples of these innovative morphologies include the specialized and diverse penetration structures (appressoria) present in many plant pathogenic fungi (Ames, 2017; Geoghegan *et al.*, 2017; Mendgen *et al.*, 1996), the mycorrhizal nutrient bridges that develop between mushroom-forming fungi and their associated plants (Bravo *et al.*, 2017; Iwaniuk and Błaszkowski, 2014; Jiang *et al.*, 2017; Marks, 2012), differentiation of wood decay models among higher fungi (Floudas *et al.*, 2012; Hibbett and Donoghue, 2001; Nagy *et al.*, 2016), and the trapping rings, nets and adhesive hyphae unique to the nematode-trapping fungi in the Orbilliomycetes (Hyde *et al.*, 2014).

Fungal models for developmental biology

Fungal species have supplied model systems that have advanced multiple disciplines. Many of the fungi selected and developed as model systems share similar features: fast growth, short life cycle, manipulability in a laboratory setting, and distinctive morphology facilitating identification. Because these traits are not unusual in fungal species, the model species are often also of direct economic importance. The best-known and most well-studied experimental fungal model species are the yeasts *Saccharomyces cerevisiae* (bread and wine yeast) and *Schizosaccharomyces pombe* (Egel, 2013; Rose, 1981), which are important tools in molecular genetics, as well as human associated *Candida* species (Ene *et al.*, 2016; Prasad, 2017). As single-celled eukaryotes, these yeasts serve as powerful model systems for the investigation of numerous fundamental principles and mechanisms, including but not limited to cell-cycle control, mitosis and meiosis tool kits, genome organization, epigenetics and epigenomics, DNA recombination and repair, signal transduction, population genetics, and the aging process (Boynton *et al.*, 2017; Caudy *et al.*, 2017; Egel, 2013; Fuchs and Quasem, 2014; Salehzadeh-Yazdi *et al.*, 2014; Tsubouchi, 2006). A global genetic interaction network based on *S. cerevisiae* provides a wiring diagram of cellular function (Costanzo *et al.*, 2016). Yeasts also are models for developmental biology, especially for cell-to-cell communication, cell polarity, and budding and mating processes, although the scope of their contributions has been restricted to cellular development (Drubin, 1991; Liti, 2014; Tomičić and Raspor, 2017; Winters and Chiang, 2016). Representatives of long-time multicellular fungal models for developmental biology include the ascomycetous species *Aspergillus nidulans* (Braus *et al.*, 2002; Croft, 1966; Seo, 2005; Timberlake, 1993) and *Neurospora crassa* (Aramayo and Selker, 2013; Davis, 2000; Davis and Perkins, 2002; Mitchell, 1955; Selker, 2017) and their closely related species, and basidiomycetous species including *Schizophellum commune* (Casselton and Kües, 2007; Essig, 1922; Wessels, 1989), *Coprinopsis cinerea* (Plaza *et al.*, 2014), and *Coprinus comatus*

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

(Casselton and Kües, 2007; Junjie-Yuan *et al.*, 2010; Winterboer and Eicker, 1983). Among these multicellular models, *N. crassa* was the first one whose genome was sequenced, a tribute to its longstanding position as a model for genetics, beginning with its role in the formulation of the "one gene–one enzyme" hypothesis proposed by Edward Tatum and George Wells Beadle (1941), who—for this insight—won the Nobel Prize in Physiology or Medicine in 1958 (Davis and Perkins, 2002). Unlike yeasts and *Aspergillus* species, *N. crassa* has little importance in medical, agriculture and food industries—although it is consumed as ontjom (Beuchat, 1976), and spurred by its model status, some have investigated its potential in biofuel development and biotechnology (Benz *et al.*, 2014; Roche *et al.*, 2014; Seibert *et al.*, 2016; Tian *et al.*, 2009). Studies of the developmental biology of *N. crassa* have been mainly focused on asexual development, although over many years, numerous sexual development- and meiosis-related genes have been characterized (Borkovich *et al.*, 2004; Iyer *et al.*, 2009; Krystofova and Borkovich, 2006; Lehr *et al.*, 2014; Springer, 1993; Springer and Yanofsky, 1992; Stajich, 2014; Vigfusson and Weijer, 1972; Wang *et al.*, 2012, 2014).

Knowledge of fungal development contributes to basic and applied sciences

Compared with most plant or animal models, the genomes of fungal model species are comparatively small and simple. Nevertheless, they retain genes for most of the core metabolism, conserved pathways, and cellular developmental regulatory mechanisms in eukaryotes (Brown, 2006). For research at the cellular development level, yeast definitely exemplifies "a model for all eukaryotic biology derives from the facility with which the relation between gene structure and protein function can be established" (Botstein and Fink, 1988, 2011). Early genetics in yeast models reaped benefits from approaches pioneered to generate biochemical mutants in *Neurospora*, which had been a model to study nitrogen, sulfur, and phosphate metabolism for eukaryotes seven decades ago (Beadle and Tatum, 1941), and more recently a model for understanding recombination, differentiation (Borkovich *et al.*, 2004), silencing and DNA methylation (Honda *et al.*, 2016), morphogenesis and cell biology (Kronholm *et al.*, 2016), and circadian rhythms (Borkovich *et al.*, 2004; Dunlap, 2008). Circadian rhythm studies in *N. crassa* resulted in the cloning of the first clock genes in the early 1980s (Dunlap *et al.*, 2007a, b). Hall and Rosbash later identified the *period* gene from fruit flies, work that led to a recent Nobel prize shared by Hall, Rosbach, and Young. Discovery of the fungal circadian system occurred more than a decade prior to the cloning of the first human clock genes (Antoch *et al.*, 1997). With the traditional gene by gene approach, a community of hard-working *Neurospora* geneticists contributed knowledge of 1100 genes with phenotypes over 60 years, before the recent high-throughput approach that produced 11,000 knockout strains providing a means to knowledge of function in over 9600 genes (Collopy *et al.*, 2010). Recent studies on *Neurospora* and *Aspergillus* shed light on how internal clock-related oscillations and asexual development are regulated in response to environmental signals in fungi (Dasgupta *et al.*, 2015; Hong *et al.*, 2014; Montenegro-Montero *et al.*, 2015; Rokas, 2013). Fungal models have also been used to understand how sex may have evolved in eukaryotes (Heitman, 2015). Many of the core methods of genomics and systems biology applied to eukaryotic systems were first developed from fungal genetics, including physical mapping, pulsed field gel electrophoresis, knockout collections, signature tagged mutagenesis, genome assembly methods, transcriptomic profiling, proteomic profiling, and genome-scale identification of protein-DNA interactions (Kück, 2013).

Other fungal models have also been examined to illuminate fungal multicellular developmental biology. For example, whether an "hourglass" model of the conservation of expression of developmentally-related genes appears in fungi like it appears in other eukaryotes (Drost *et al.*, 2015; Kalinka *et al.*, 2010; Ninova *et al.*, 2014; Quint *et al.*, 2012) was investigated using the model mushroom-forming fungus *C. cinerea* (Cheng *et al.*, 2015). *Aspergillus* species have been intensively studied for their asexual growth—mainly because secondary metabolic products, such as mycotoxins, antibiotics and citric acids, are enriched during late asexual development (Adams and Yu, 1998; Bayram *et al.*, 2016; Garzia *et al.*, 2013; Keller, 2006; Yin *et al.*, 2013). Some fungi do not form fruiting bodies in laboratory conditions, implying that unknown environmental factors are involved in the growth and development in these fungi. For instance, metagenomic evidence suggests that the composition of bacterial communities is associated with the differentiation and development of sexual structures in black truffle fungus (Antony-Babu *et al.*, 2014). Once the genome sequencing of *N. crassa* was complete (Galagan *et al.*, 2003), genome sequences of *Aspergillus* species (Galagan *et al.*, 2005; Machida *et al.*, 2005; Nierman *et al.*, 2005; Ronning *et al.*, 2005; Yu *et al.*, 2005), *Magnaporthe oryzae* (Dean *et al.*, 2005), and *Fusarium graminearum* (Cuomo *et al.*, 2007) quickly followed. These core filamentous ascomycete species established a jumping board to study previously intractable species and elucidate host–pathogen interactions in both human and plants, development of infection-associated structures, and hyphal development and sporulation, both as conidia and sexual fruiting bodies. These advances in core filamentous species enabled study of development and sporulation in the obligately biotrophic pathogens such as rusts (Cuomo *et al.*, 2007; Yin *et al.*, 2015) and powdery mildews, and to determine the adaptive genome evolution of *Malessizia*, the human skin pathogen in the Ustilaginomycotina, a subphylum of predominantly plant smut fungi (Wu *et al.*, 2015). Study of fungal development has led to the realization that regulation of secondary metabolite production and development are correlated (Keller *et al.*, 2005), and the global regulator complex, VelB/VeA/LaeA, that coordinates light signaling with development also regulates secondary metabolism through chromatin remodeling mediated by LaeA (Bayram *et al.*, 2016). Very recently, regulators of the stages of asexual sporulation have been shown to also regulate the genes for secondary metabolites that accumulate during those stages of development (Lind *et al.*, 2017).

2. Study of fungal development and its evolution

Development of fungi has received considerable attention in the form of high-level analyses of the systematics and

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

classification of fungi, that map evolutionary developmental characteristics to taxonomy. Indeed, from early 17th century, most studies on fungal development and its evolution had to depend solely on morphology and anatomical evidence (Bary et al., 1887; Drews, 2001), eventually including ultrastructural characters. Because of this confounding dependence, relationships between morphological development and evolution were long considered as a black box that could not be directly investigated. However, longstanding knowledge from morphological studies continues to supply ideas, hypotheses, and research questions about fungal development that now can be investigated using molecular probes. Consequent advances in fungal phylogeny and phylogenomics have dramatically improved our knowledge about relationships among various fungal lineages and within taxa. These solved phylogenies make it possible to precisely reconcile the evolution of morphological diversity and genetic diversity in fungi (Dornburg et al., 2017; McCarthy and Fitzpatrick, 2017; Nagy and Szöllősi, 2017; Zhang et al., 2017).

Traditional gene by gene approaches to the evolution of development

Significant effort and resources have been spent performing genetic perturbations to reveal developmental phenotypes in various fungal models, and important breakthroughs have been extensively reviewed (Chiu and Moore, 1996; Esser and Lemke, 1994; Kües and Fischer, 2006; Lehr et al., 2014; Meinhardt and Wessels, 2013; Nowrousian, 2014; Osiewacz, 2002; Sikhakolli et al., 2012; Trail, 2013; Wendland, 2016). Sequenced genomes of fungal models have recently accelerated the molecular identification of genetic markers phenotypically identified via traditional mutant screens (Riquelme and Martínez-Núñez, 2016). In one example, McCluskey et al. (2011) examined 18 classical mutant strains in *N. crassa*, readily identifying all of them to their causative DNA mutation using whole genome sequencing. Genome sequencing and annotation of increasing numbers of non-model species has also enabled technologies that facilitate the investigation of molecular developmental biology in non-model organisms. Nevertheless, reductive gene by gene approaches to assess genetic basis of development processes have been limited by several issues: genes may have multiple phenotypes, including fatal ones; several genes may have redundant functions for certain developmental phenotypes or in certain environments; discovery of phenotypes for individual genes may require specific genetic and environmental settings that are not easily known; and lastly, the development of complexity and its regulation is widely believed to involve interactions of many genes through gene-networks that are sparsely revealed by associations detected between single genes and single developmental phenotypes (Cheng et al., 2013; Le Nagard et al., 2011; Li and Johnson, 2010; Macía et al., 2011; Payne and Wagner, 2014). In addition, one of the biggest hurdles to finding genes involved in a particular process is the selection of the genes that are to be functionally assayed: candidate gene lists are often short to nonexistent, as well as challenging to prioritize. Prediction is critical, because molecular genetic assays entail extensive effort, in filamentous fungi requiring recovering a single genetically pure cell for each putative manipulation. Depending on the gene expression effects that one is trying to investigate, one must also choose among diverse potential experiments, such as directed mutation to abrogate function, knockout, knock-down, and knock-up experiments. To phenotype putative mutants for complex traits such as fruiting body development, each putative transformant must be grown under conditions that induce fruiting bodies. Then the fruiting bodies must be examined (by sectioning and microscopy) to determine whether development has been affected (Collopy et al., 2010; Colot et al., 2006; Fu et al., 2011; Lord and Read, 2011; McCluskey and Plamann, 2008; Teichert et al., 2012; Trail, 2013).

Evolutionary genomics and transcriptomics of fungal development

Genome-wide approaches have recently exhibited promise in resolving some puzzles in fungal development and its evolution, especially developmental traits regulated by genes conserved in ontology (Maheshwari, 2016). Filamentous fungi typically feature about 15,000 genes; knocking them all out and characterizing them is a monumental task. High throughput systems still require the conscientious examination of individual knockouts throughout the life cycle, and without guidance as to which stages are the relevant ones to look at, highly relevant phenotypes are easily missed. A common strategy for the study of the evolution of development in model organisms begins with identification of possible genes and gene networks that respond to a developmental process (genotyping to phenotyping) in one or several species (models), and then proceeds to identification of conserved elements along the evolutionary history of the developmental traits (Bolker, 2014). In fact, assessment of the components of a gene network underlying a developmental process using genome-wide approaches requires extensive foreknowledge of the genetic basis of the investigated process, usually derived from previous gene-by-gene studies. Detailed genetic knowledge obtained regarding the cell walls of yeast model systems has empowered comparative genomic analyses that contribute fundamental understanding of their evolution in fungi (Ruiz-Herrera and Ortiz-Castellanos, 2010; Xie and Lipke, 2010). A pioneering study combined a time course of genome-wide gene expression on a single species and gene knockout to assess gene function in model *S. cerevisiae* (DeRisi et al., 1997; Díaz et al., 2009; Lashkari et al., 1997). Knockout phenotyping has been used to understanding gene functions in filamentous fungi, especially for many mutants created by target nonspecific approaches, and many of these studies focused on genes known to exhibit similar function or known to be involved in related pathways or networks (Chai et al., 2016; Collopy et al., 2010; Engh et al., 2010; Fu et al., 2014, 2011; Kopke et al., 2010; Lehr et al., 2014; Nowrousian and Cebula, 2005; Schindler and Nowrousian, 2014; Teichert et al., 2016; Watters et al., 2011). Recently, transcriptomic data across sexual development helped to infer a network of meiotic silencing genes, which were individually characterized for function in perithecial development based on their knockout phenotypes in *N. crassa* (Wang et al., 2014). Interestingly, peak expression during wild type perithecial development was perfectly reversed from their genetically determined order of operation in meiotic silencing, indicating a discrepancy between their

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

functional order in wild type development and in the event of meiotic silencing. That match between expression regulation and expected knockout phenotype epitomizes how good practice of a focused knockout strategy can be especially informative. Regulatory networks and their expression are likely conserved for orthologous developmental traits—especially key developmental characters among species sharing the development processes. Comparing fungal species for their genomics and transcriptomics consensus during the development of the same traits has been used to infer the genetic basis of fungal biology (Chibucos *et al.*, 2016; Gan *et al.*, 2012; Ge *et al.*, 2016), a genomic approach that provides an alternative for identifying genes behind common development traits. Arboretum, a program that integrates evolutionary genomics and transcriptomics to assess shared developmental co-expression traits among species, has been applied to yeast groups (Knaack *et al.*, 2016; Roy *et al.*, 2013).

However, fungi exhibit a huge diversity in morphology, and little of this phenotypic diversity can be examined by starting with model species and the integrative approaches mentioned above. In theory, differences in developmental traits among diverse species can be explained by differences in gene regulation and expression that evolved along the taxon phylogeny (Demidenko and Penin, 2012; Kalinka *et al.*, 2010; Shestakova, 2015; West-Eberhard, 2003). Therefore in principle, the candidate gene pool for phenotyping morphological differences on traits can be narrowed down—and prioritized—using comparative genomics and transcriptomics. Differences in expression of orthologous genes along their evolutionary history are likely to contribute to developmental differences among homologous morphological traits. Under this view, reconstruction of ancestral gene expression phenotypes would facilitate identification of genes with the largest evolved increases in gene expression across development, which in turn would likely be involved in relevant phenotypic novelties. Guidance provided by this logic could lead to discovery of relevant genes more efficiently than other gene deletion studies targeting whole genomes or gene families.

Such a strategy for pinpointing genes responsible for the evolution of certain biological processes has recently been developed using the fungi *N. crassa* and *Fusarium graminearum*, models for perithecium development, as well as species closely related to these fungi (Trail *et al.*, 2017). Ancestral gene expression states, including ancestral changes across sexual development, were inferred for five related species during comparable stages of sexual development. An association between genes whose transcription has been substantially and significantly altered during the evolutionary process and phenotypes that change along the same phylogenetic branch was validated by performing functional studies: gene disruption that frequently resulted in substantial changes in fruiting body development in the disruptants at morphological stages when the wild type gene's expression shift was divergent between species (Trail *et al.*, 2017). Many genes that relate to novel phenotypes in the development of fungal fruiting bodies can be predicted and prioritized for focused knockout phenotyping by estimating which genes have increased their expression recently in evolutionary time. To do so, genome-wide gene expression should be measured for distantly related fungal species during the same developmental process, where a highly similar sexual morphology evolved with distinct species-specific characters among these species. Ancestral expression can then be calculated by diverse means (Cooper *et al.*, 2015; Joy *et al.*, 2016; Rohlfs *et al.*, 2013), including using a Continuous Ancestral Character Estimation (CACE) that assumes that traits evolve according to a Brownian motion process (Schluter *et al.*, 1997), a calculation for which there is an available R package, Analyses of Phylogenetics and Evolution (APE (Paradis, 2011; Paradis *et al.*, 2004)). Such a guided knockout approach demonstrated a significantly higher efficiency than traditional systematic knockout approach in identifying genes that may be responsible for observed developmental differences as applied in *Neurospora* and *Fusarium* (Trail *et al.*, 2017). The study demonstrates a precision shortcut for researchers: if they first identify identical genes present across different species that have recently evolved and increased in gene expression, they can knock out or otherwise perturb this smaller targeted set to reveal genes that underlie a phenotype of interest in a specific species (Fig. 1). Predictions provided by the evolutionary analysis of gene expression enabled identification of genes that were likely to exhibit a knockout phenotype involved in any process, even if complex and understudied.

The power of this approach for understudied species lies in the pairing of well-studied organisms with phylogenetically close organisms that are not so well studied. The requirements for inclusion of species are that they must have a

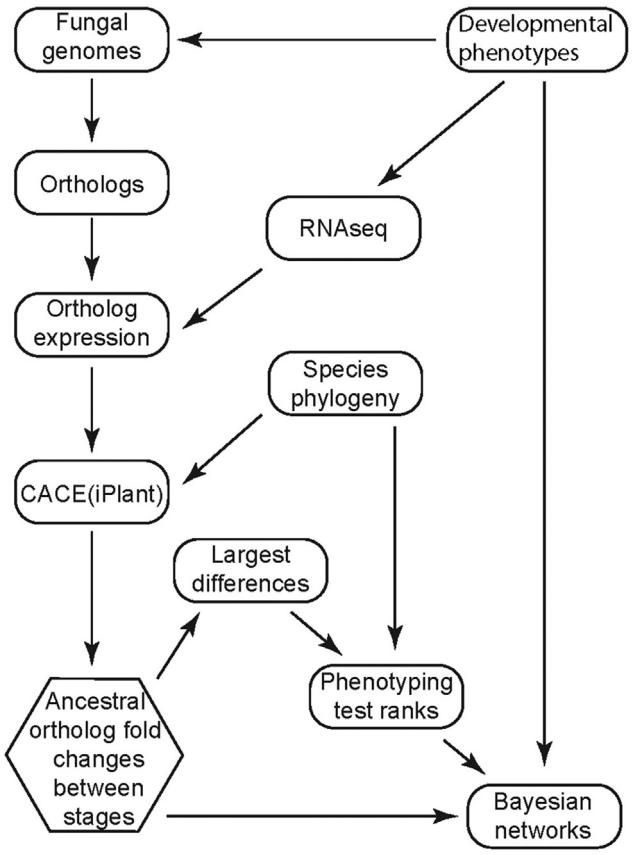

Fig. 1 – Flow chart for ancestral ortholog predictions, RNA-seq, phylogeny, and focused knockout phenotyping (modified from Trail *et al.*, 2017).

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

genome sequence, and they must be able to be cultured in a common environment, yielding extractable mRNA from homologous stages of development. Although an averaging of mRNAs in organisms that develop asynchronously makes the technique remain applicable to populations that exhibit developmental stochasticity, the results are more powerful for organisms that can be manipulated to develop synchronously (Trail *et al.*, 2017). The process has been demonstrated to be highly effective for gene discovery of conidial germination and plant penetration and can be effective even when conidia are collected while germinating on a diversity of host plants (Trail *et al.*, 2017). Thus, even though inference of the evolution of gene expression is formally compromised by growth on different substrates, it appears that the use of an evolutionary approach on data gathered from heterogeneous but functionally analogous environments can still empower the discovery of genes of functional importance during the developmental process.

This transcriptomic evolution of development approach worked just as well for unannotated genes: among the candidate genes identified for further phenotyping investigation are many whose functional identification has been lacking. In fact, whole genome screening for sexual development mutants had already been performed for *Neurospora;* nevertheless, most the phenotype assignments to *N. crassa* genes reported in Trail *et al.* (2017) are new. While the whole-genome screen can be productive, focused knockout can be a powerful and complementary form of investigation. Moreover, to date only one filamentous fungus had been subject to a whole genome knockout project—such undirected studies are challenging to fund. Trail *et al.* (2017) provide a strategy that can identify targets for knockout and phenotyping in multiple species at once, reducing the effort required to identify genes playing a role in a particular process, and addressing relevant hypotheses regarding the evolution of morphologies of interest. Gathering expression and morphological data confers independent benefits for transcriptomic and evolutionary studies, and provides synergies with knockout phenotype data. It is likely (if not inevitable) that there will be increasing numbers of comparative studies, empowered by genome sequencing and modern knockout technologies, examining the function of gene knockouts across suites of related species featuring divergent morphologies. Performing these knockouts in a principled and efficient way should be attractive to everyone, but especially to anyone with interest in the evolution of development. This approach is poised to take on a larger and larger role within that field.

3. Conceptual and practical strategies to systems biology of fungal development

While identification of genes to examine can be aided by consideration of evolutionary dynamics of gene expression across phylogenies, refinement of models of those gene interactions within individual species requires a more focused approach. Traditional reductionist approaches of gene-by-gene methodologies are laborious and tend to lead to overly linear description, and genomic inference from comparative genomics and transcriptomic data alone have little power to reveal the details of the complex processes of macroscopic development. Systems biology, an emerging holistic interdisciplinary approach, is a biology-based field of study that focuses on complex interactions within biological systems (Albrecht and Guthke, 2009; Kaneko, 2006; Marcum, 2009). Systems developmental biology has attracted considerable attention and inspired funding opportunities (Perrimon and Barkai, 2011). Systems biology is the integration of many observations to understand the emergent functions of complex adaptive modules. To reveal the complex, dynamic and nonlinear systemic architecture of development, a systems biology approach can be used to incorporate mathematical interval analysis and model discrimination analysis (Benfey, 2011; Boogerd *et al.*, 2007; Ideker *et al.*, 2001). This approach consists of 1) identifying dynamically relevant parts of the system, 2) creation of one or more model hypotheses of the interaction among these parts, 3) application of these models on high-throughput data to initiate a working hypothesis, 4) identification of the most effective perturbation steps to verify and to improve the initial hypothesis, and 5) evaluation and revision of the model hypothesis to refine the set of putative models to be verified with phenotypic data and gene manipulation.

Develop criteria to guide systems biology for developmental questions using N. crassa

N. crassa has been a productive genetic model organism, with continued promise for revealing the molecular basis of the complex metabolic and morphological changes associated with sexual development of fungi (Bistis *et al.*, 2003; Borkovich *et al.*, 2004; Lord and Read, 2011; Selker, 2011). The *Neurospora* research community also has constructed and made available over 11,000 knockout strains for more than 9600 genes (Dunlap *et al.*, 2007a, b). Previous research on *N. crassa* has yielded knowledge, data and tools that facilitate the study of the genetic basis of asexual growth and development (Iyer *et al.*, 2009; Krystofova and Borkovich, 2006; Pöggeler, 2011; Rodriguez-Romero *et al.*, 2010; Springer, 1993; Springer and Yanofsky, 1992; Vigfusson and Weijer, 1972; Wang *et al.*, 2012, 2014; Whittle and Johannesson, 2011).

Analyses of gene expression and genetic regulatory networks in diverse model organisms have demonstrated that genes work together in response to regulatory factors to shape metabolic processes and morphological development as well as aging (Freeman *et al.*, 2012; Guo *et al.*, 2011; Huang *et al.*, 2012; Judge *et al.*, 2017; Tong, 2004). For example, a study just published shows that evolution of the fungal polarization network is highly dynamic but functionally conserved through structural conservation in polarization protein networks (Diepeveen *et al.*, 2017). However, further investigation of any putative network requires hypothetical prediction on the basis of heterogeneous data arising from diverse experimental designs, missing information, and limited prior knowledge (Emmert-Streib and Glazko, 2011; Zarringhalam *et al.*, 2013). One classification of gene networks that can be developed for genome-wide time-series data (Barman and Kwon, 2017; Kim *et al.*, 2004; Park *et al.*, 2017; Zamanighomi *et al.*, 2014) divides them into three categories: gene co-expression networks (GCNs) using continuous data (López-Kleine *et al.*, 2013), gene regulatory networks (GRNs) using

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

discrete data (Hecker *et al.*, 2009), and Bayesian networks (BNs), which allow both data types, thus making it particularly feasible to integrate genetic and environmental factors into predictions (Ziebarth *et al.*, 2013; Ziebarth and Cui, 2016). Regardless of how a gene network model is inferred, prior knowledge of gene associations to be investigated should be gathered from literature and data mining, and some level of experimental validation is always needed (Hecker *et al.*, 2009). Yeast model species are among the best-studied fungal models, and most recent knowledge about fungal metabolism pathways and cellular development networks has been revealed using yeast models (Mustacchi *et al.*, 2006). The complex interactions between fungi and their hosts have also been the subject of extensive experimental investigation. An early genome-wide GRN network model revealed interactions between host and fungal pathogen *Candida albicans* (Altwasser *et al.*, 2012) and *Aspergillus fumigatus* (Guthke *et al.*, 2016). Unlike GCNs and GRNs that use comparatively simple strategies for large network construction, BNs sacrifice network size for probabilistic robustness, making them more suitable for assessing central subnetworks and their dynamics within a larger gene network (Young *et al.*, 2014). A BN was inferred for associations during sexual development and meiosis silencing in *N. crassa* using gene expression data, and knockout phenotypes showed high consistency between the order of the morphological development and tie structure of the predicted network (Wang *et al.*, 2014). In the near future, genome-scale metabolic networks that are mechanistic in nature are expected to be able to be reconstructed with high precision and robustness (Al-Omari *et al.*, 2015; Oguz *et al.*, 2017). But for the level of complexity underlying evo-devo, both statistical networks such as Bayesian networks and molecular biological mechanistic networks are likely to continue to play roles for different levels of underlying knowledge and to complementarily reveal unknown network topology for developmental complexity.

The probabilistic formalism in Bayesian Network (BN) provides a robust and straightforward approach toward modeling the highly interactive components that are key to biological systems (Needham *et al.*, 2006, 2007). However, to explore an unknown complex using Bayesian networks requires the development of the means for quantitatively describing and comparing networks—especially the dynamic changes in networks (de Luis Balaguer and Sozzani, 2017; Ghanmi *et al.*, 2011; Li *et al.*, 2011). In addition, quantitative and qualitative characteristics of BN, including the probabilistic and mechanistic models, make it possible to precisely manipulate components of the network *in silico* before verifying them *in vitro*. Regarding investigation of genetic networks in fungal biology and development, a Maximally Informative Next Experiment (MINE), conceptually defined as the maximum distance (by some quantitative metric) between model-determined networks, provided predictions of the optimal perturbations to study the dynamics of a circadian network in *N. crassa* (Dong *et al.*, 2008). In this well-studied system, the action kinetics of circadian dynamics can be directly quantitatively measured, and the elegantly parameterized circadian network could be modeled with ordinary differential equations (ODE) representing the temporal profiles of genes and their products (Dong *et al.*, 2008). Unlike the metabolic networks underlying circadian rhythms that can be quantified using established biochemical modeling approaches, developmental regulatory networks remain challenging to quantitatively describe using ODEs. The MINE concept, however, is general, and can be adapted to measure the robustness difference (posterior possibility space difference) of more statistical modeling approaches such as Bayesian networks, and thus be applied to predict the maximally informative next experiment.

Systems biology strategy to study fungal development using Bayesian network approach

Here, we develop the idea of systematically proposing experiments via robust Bayesian network ensemble modeling, with our focus on the identification of the maximally informative next experiment in fungal development. Generally, model parameters can be perturbed in accordance with experimental capabilities. The diversity of outcomes in response to each perturbation across the ensemble of individual models can be measured by the variance in predicted progression of development. The key idea is that the experiment with the highest diversity of predicted outcomes among best models is the one that will be most informative once the experimental result is known, as it will invalidate the greatest number of otherwise high-scoring models in the ensemble. The method above falls into the framework of active learning, and specifically corresponds to the querying strategy of uncertainty sampling to estimate the topology and parameters of a Bayesian network (Ness *et al.*, 2017; Pauwels *et al.*, 2014; Tong and Koller, 2001). At each step of the training process, the expected uncertainty of each experiment given the current posterior distribution of the graph parameters is calculated and the one with the highest expected uncertainty is chosen. Thus through several iterations of the systems approach we expect the posterior distribution over the model parameters to concentrate in a small subspace, ultimately narrowing down to one or a few strongly supported models to investigate with detailed molecular biological approaches.

This rapid narrowing of the plausible set of models down to one or a few that can be further investigated with gene-by-gene molecular biological techniques represents an optimal working strategy considering the supralinear complexity of a biological network with increasing numbers of network elements. Such an experimental process should combine iterative Bayesian network modeling, transcriptomics, and knockout phenotyping led by optimizing informativeness of genetic experiments on the developmental biology (Fig. 2). Genome-wide network reconstruction approaches, such as GeCON using preliminary expression data collected and available prior knowledge from reference search and data mining can be used to identify a set of components (Roy *et al.*, 2014) module extraction—algorithms for describing subnetwork space and modularity with edge density and strength—can then be used to identify a core set of interacting genes with a proper size (He *et al.*, 2017). Three systems biological operations would then be expected to be implemented iteratively: 1) assembly of a number of BNs for the identified core network, 2) evaluation of the diversity of predictions from all putative experiments to infer a MINE, which would most successfully discriminate among models, and 3) performance of the

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

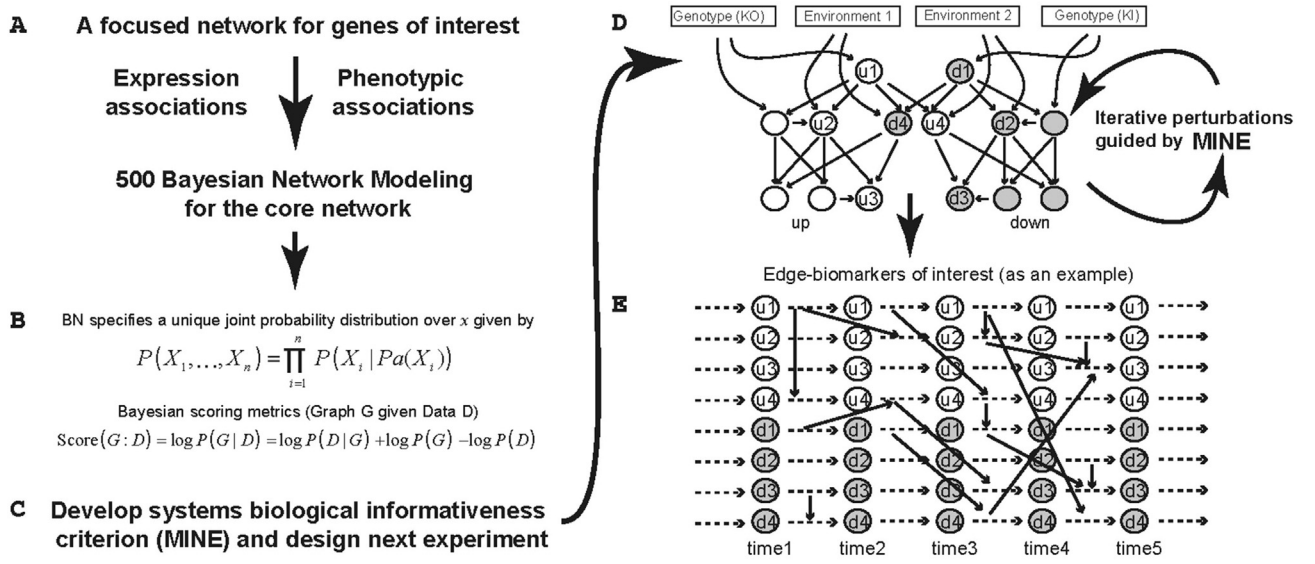

Fig. 2 – Demonstration of Bayesian Network (BN) modeling strategy in the study of fungal development. A) Mined diverse sources of data to compose an initial model. B) Guide iterative perturbations and time-course experiments using a Maximally Informative Next Experiment (MINE) criterion (c.f. Dong *et al.*, 2008). Bayesian scoring metrics can be defined with a graph *G* and data *D*. *P(G)* denotes the prior distribution of the graph, *P(D|G)* the likelihood function, and *P(G|D)* the posterior distribution of the graph given the observed data *D*. At each iteration, BNs can be constructed to describe network function based on experimentally manipulable input functions of developmental stages and other non-genetic factors, as well as quantitative output of development traits. C) Design the next experiment, prioritizing those experiments predicted to yield diverse outcomes (morphological phenotypes and/or gene expression levels) based on the current ensemble of BNs. D) Iterate genetic and environmental perturbation experiments. A core of eight genes are depicted here with up- (white circles) or down-regulated (grey circles) expression. E) Infer dynamic edge associations within the Bayesian networks using time course data. Significant associations and covariances can be handled by using dynamic edge-network approaches.

experiment directed by a MINE criterion, and assessment of gene perturbation phenotypes. Next, one returns to step 1 again, taking newly generated data combined with previous data to construct a refined ensemble core network. These steps can be iterated until no significant information is obtained by conducting the predicted best experiment.

Such systems biology approaches can be further developed and applied at a lower level of fungal evo-devo to understand the evolution of the core regulatory complex during cell and tissue type differentiation (Arendt *et al.* 2016). Although most fungal structures are microscopic, as in *N. crassa*, they are nevertheless composed of multiple cell and tissue types (Bistis *et al.*, 2003). These microscopic structures have been challenging to examine until recently, with the development and application of laser dissection (Teichert *et al.* 2012) and single cell sequencing (Picelli 2017). Unlike macroscopic forms in morphological development, homology among cell and tissue types is often comparatively easier to establish, especially within closely related fungal species. Thus, the network of regulatory interactions governing their microscopic morphology will be of high interest to molecular geneticists and synthetic biologists.

Reconciling the evolutionary histories between the developmental networks and developmental traits

Developmental biology has been informed based on investigations using the tools of molecular biology and genetics, and also by the historical inference tools of evolutionary biology. A better understanding of systems biology in fungal developmental traits would be achieved with explicit reconciliation between functional/developmental networks and their evolutionary histories. In fact, species and gene phylogenies can reveal how certain developmental traits may have converged or diverged, and thus direct comparative genomics analyses that identify candidate genes underlying the development of traits. While it has been common for systems biological analyses of expression to inform networks of interest (Cracraft, 2005; Fu *et al.*, 2017; Lu *et al.*, 2014; Nowrousian, 2014; Teichert *et al.*, 2014; Zhang *et al.*, 2015), systems biological analyses examining multiple species and inferring historical patterns of gene expression can help to define the evolution of developmental networks of interest. Reconstruction of historical genetic networks along the species phylogeny could be especially helpful in illuminating genetic components of developmental traits that are regulated, often quantitatively or plastically, by multiple genes—whereas gene-by-gene phenotype analysis is only slowly, step by step, informative for inferences regarding multiple gene–gene interactions (Li and Johnson, 2010; Shamir, 2008).

Comparative genomic data to identify orthologous genes, comparative transcriptomic data to reconstruct evolutionary changes of gene expression phenotypes across multiple species, and gene knockout technology in more than one species to interrogate function, can be pursued to bring comparative

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

genetics, developmental biology, genomics, and transcriptomics into a single phylogenetic framework. In Trail *et al.* (2017), genetic networks during perithecial initiation and perithecial beak development were inferred using Bayesian network approach and compared among five Sordariomycetes models. Results showed that a core network of orthologous developmental processes is probably conserved in component and expression regulation among morphologically divergent species. Similarly, conserved involvement in mushroom development of transcriptional circuitry consisting of a few orthologous genes was suggested by a comparative transcriptomics on the model mushroom *C. cinerea* (Plaza *et al.*, 2014). Reconciliation among multiple species of the gene network and associated developmental traits—"syst-evo-devo" would directly bridge the hallowed terrains of morphological divergence and genetic/genomic/transcriptomic adaptation. This reconciliation is not just of disciplinary interest for fungal systematics and evolution, but also promises significant returns for investigators involved in other aspects of mycology—especially investigators working on fungal groups of special ecological and economic value. These fungi include many pathogens and industrial species that generally exhibit highly reduced morphology. Understanding the regulatory basis of the extant morphology and its relation to complex morphologies in model organisms would be critical for further work revealing key genes responsible for developmental transitions to stages of fungal life history that are of particular interest.

4. Concluding remarks on fungal development: past, present and future—reductive approaches to integrative systems biology strategies

Advances in quality and quantity from genomics and transcriptomics data, and simultaneous methodological advances associated with systems biology approaches, has the potential to lead to a new era for evolutionary developmental biology in diverse fungal species. Especially for most development phenotypes that are controlled by multiple factors modulated by a regulatory network, evolutionary systems biology provides a means to infer evolution of the regulatory network underlying developmental traits and to provide strategies to quantitatively and qualitatively verify functional roles of key components of the network. Developmental biology can now advance beyond a reductive molecular biological investigation that is heavily dependent on a pre-set understanding of development traits, which generally requires extensive trial experiments and complicated strategies of investigation that sacrifice statistical power for robustness of a few key findings. Recent advances in fungal genomics and transcriptomics greatly improve the efficiency of reductionist approaches by supplying focused targets for manipulations, yet investigation of regulatory networks for various developmental traits faces many challenges that are beyond the scope of gene-by-gene approaches. Integrating systems biology into evo-devo can provide solutions to those challenges, since systems biology can rapidly incorporate the many components of the developmental process that are naturally in operation. Moreover, systems biology approaches can catalog key components of development into statistically optimal groups based on all available data from genetics, transcriptomics and evolutionary biology with large-scale computational intelligence, to significantly and rationally improve experimental strategies and efficiency. Gene regulatory networks incorporating time course expression data, comparative genomics, and species phylogeny make it possible to integrate reductive approaches and systems biology for understanding fungal development within an evolutionary frame. Dynamic model-based iterative experiment is a promising strategy toward revealing the genetic basis of fungal morphological development and its evolution.

> *"Nevertheless, genomics marks a shift away from the extreme reductionism of molecular biology, and allows insights into biological complexity never before possible. The whole is, indeed, greater than the sum of its parts."* (Bennett and Arnold 2001)

Declaration of interest

The authors declare no competing interests.

Acknowledgements

We thank our editor Dr. Laszlo Nagy and two anonymous reviewers for their constructive suggestions. This work was supported by the Agriculture and Food Research Initiative competitive grant program, no. 2015-67013-22932 from the USDA National Institute of Food and Agriculture to FT and JPT and by the National Science Foundation (IOS 1457044) to JPT and IOS 1456482 to FT. We acknowledge funding from MSU AgBioResearch to FT.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fbr.2018.02.001.

REFERENCES

Adams, T.H., Yu, J.-H., 1998. Coordinate control of secondary metabolite production and asexual sporulation in *Aspergillus nidulans*. Curr. Opin. Microbiol. 1, 674–677.

Albrecht, D., Guthke, R., 2009. Systems biology of human-pathogenic fungi. In: Handbook of Research on Systems Biology Applications in Medicine. IGI Global, pp. 403–421.

Alexopoulos, 2007. Introductory Mycology, fourth ed. John Wiley & Sons.

Al-Omari, A., Griffith, J., Judge, M., Taha, T., Arnold, J., Schuttler, H.-B., 2015. Discovering regulatory network topologies using ensemble methods on GPGPUs with special reference to the biological clock of *Neurospora crassa*. IEEE Access 3, 27–42.

Altwasser, R., Linde, J., Buyko, E., Hahn, U., Guthke, R., 2012. Genome-wide scale-free network inference for *Candida albicans*. Front. Microbiol. 3, 51.

Ames, R.M., 2017. Using network extracted ontologies to identify novel genes with roles in appressorium development in the

rice blast fungus *Magnaporthe oryzae*. Microorganisms 5. https://doi.org/10.3390/microorganisms5010003.

Antoch, M.P., Song, E.-J., Chang, A.-M., Vitaterna, M.H., Zhao, Y., Wilsbacher, L.D., Sangoram, A.M., King, D.P., Pinto, L.H., Takahashi, J.S., 1997. Functional identification of the mouse circadian clock gene by transgenic BAC rescue. Cell 89, 655–667.

Antony-Babu, S., Deveau, A., Van Nostrand, J.D., Zhou, J., Le Tacon, F., Robin, C., Frey-Klett, P., Uroz, S., 2014. Black truffle-associated bacterial communities during the development and maturation of *Tuber melanosporum* ascocarps and putative functional roles. Environ. Microbiol. 16, 2831–2847.

Aramayo, R., Selker, E.U., 2013. *Neurospora crassa*, a model system for epigenetics research. Cold Spring Harb. Perspect. Biol. 5 a017921.

Barman, S., Kwon, Y.-K., 2017. A novel mutual information-based Boolean network inference method from time-series gene expression data. PLoS One 12 e0171097.

Bary, A., de Balfour, I.B., Garnsey, H.E.F., 1887. In: de Bary, A., Balfour, I.B. (Eds), Comparative Morphology and Biology of the Fungi, Mycetozoa and Bacteria. Clarendon Press, Oxford.

Bateson, W., 1922. Evolutionary faith and modern doubts. Science 55, 55–61.

Bayram, Ö., Feussner, K., Dumkow, M., Herrfurth, C., Feussner, I., Braus, G.H., 2016. Changes of global gene expression and secondary metabolite accumulation during light-dependent *Aspergillus nidulans* development. Fungal Genet. Biol. 87, 30–53.

Beadle, G.W., Tatum, E.L., 1941. Genetic control of biochemical reactions in *Neurospora*. Proc. Natl. Acad. Sci. USA 27 (11), 499–506.

Benfey, P.N., 2011. Taking a developmental perspective on systems biology. Dev. Cell 21, 27–28.

Bennett, J.W., Arnold, J., 2001. Genomics for fungi. In: Biology of the Fungal Cell, pp. 267–297.

Benz, J.P., Chau, B.H., Zheng, D., Bauer, S., Glass, N.L., Somerville, C.R., 2014. A comparative systems analysis of polysaccharide-elicited responses in *Neurospora crassa* reveals carbon source-specific cellular adaptations. Mol. Microbiol. 91, 275–299.

Beuchat, L.R., 1976. Fungal fermentation of peanut press cake. Econ. Bot. 30, 227–234.

Bistis, G.N., Perkins, D.D., Read, N.D., 2003. Different cell types in *Neurospora crassa*. Fungal Genet. Rep. 50, 17–19.

Blackwell, M., 2011. The fungi: 1, 2, 3… 5.1 million species? Am. J. Bot. 98, 426–438.

Bolker, J.A., 2014. Model species in evo-devo: a philosophical perspective. Evol. Dev. 16, 49–56.

Boogerd, F., Bruggeman, F.J., Hofmeyr, J.-H.S., Westerhoff, H.V., 2007. Systems Biology: Philosophical Foundations. Elsevier.

Borkovich, K.A., Alex, L.A., Yarden, O., Freitag, M., Turner, G.E., Read, N.D., Seiler, S., Bell-Pedersen, D., Paietta, J., Plesofsky, N., Plamann, M., Goodrich-Tanrikulu, M., Schulte, U., Mannhaupt, G., Nargang, F.E., Radford, A., Selitrennikoff, C., Galagan, J.E., Dunlap, J.C., Loros, J.J., Catcheside, D., Inoue, H., Aramayo, R., Polymenis, M., Selker, E.U., Sachs, M.S., Marzluf, G.A., Paulsen, I., Davis, R., Ebbole, D.J., Zelter, A., Kalkman, E.R., O'Rourke, R., Bowring, F., Yeadon, J., Ishii, C., Suzuki, K., Sakai, W., Pratt, R., 2004. Lessons from the genome sequence of *Neurospora crassa*: tracing the path from genomic blueprint to multicellular organism. Microbiol. Mol. Biol. Rev. 68, 1–108.

Botstein, D., Fink, G., 1988. Yeast: an experimental organism for modern biology. Science 240, 1439–1443.

Botstein, D., Fink, G.R., 2011. Yeast: an experimental organism for 21st century biology. Genetics 189, 695–704.

Boynton, P.J., Janzen, T., Greig, D., 2017. Modeling the contributions of chromosome segregation errors and aneuploidy to *Saccharomyces* hybrid sterility. Yeast. https://doi.org/10.1002/yea.3282.

Braus, G., Krappmann, S., Eckert, S., 2002. Sexual development in Ascomycetes fruit body formation of *Aspergillus nidulans*. In: Molecular Biology of Fungal Development.

Bravo, A., Brands, M., Wewer, V., Dörmann, P., Harrison, M.J., 2017. Arbuscular mycorrhiza-specific enzymes FatM and RAM2 fine-tune lipid biosynthesis to promote development of arbuscular mycorrhiza. New Phytol. 214, 1631–1645.

Brown, A.J.P., 2006. The Mycota: a Comprehensive Treatise on Fungi as Experimental Systems for Basic and Applied Research. Springer Verlag.

Casselton, L.A., Kües, U., 2007. The origin of multiple mating types in the model mushrooms *Coprinopsis cinerea* and *Schizophyllum commune*. In: Sex in Fungi, pp. 283–300.

Caudy, A.A., Mülleder, M., Ralser, M., 2017. Metabolomics in yeast. Cold Spring Harb. Protoc. 2017 db.top083576.

Chai, H., Yin, R., Liu, Y., Meng, H., Zhou, X., Zhou, G., Bi, X., Yang, X., Zhu, T., Zhu, W., Deng, Z., Hong, K., 2016. Sester-terpene ophiobolin biosynthesis involving multiple gene clusters in *Aspergillus ustus*. Sci. Rep. 6, 27181.

Cheng, C.K., Au, C.H., Wilke, S.K., Stajich, J.E., Zolan, M.E., Pukkila, P.J., Kwan, H.S., 2013. 5′-serial analysis of gene expression studies reveal a transcriptomic switch during fruiting body development in *Coprinopsis cinerea*. BMC Genom. 14, 195.

Cheng, X., Hui, J.H.L., Lee, Y.Y., Wan Law, P.T., Kwan, H.S., 2015. A "developmental hourglass" in fungi. Mol. Biol. Evol. 32, 1556–1566.

Chibucos, M.C., Soliman, S., Gebremariam, T., Lee, H., Daugherty, S., Orvis, J., Shetty, A.C., Crabtree, J., Hazen, T.H., Etienne, K.A., Kumari, P., O'Connor, T.D., Rasko, D.A., Filler, S.G., Fraser, C.M., Lockhart, S.R., Skory, C.D., Ibrahim, A.S., Bruno, V.M., 2016. An integrated genomic and transcriptomic survey of mucormycosis-causing fungi. Nat. Commun. 7, 12218.

Chiu, S.-W., Moore, D., 1996. Patterns in Fungal Development. Cambridge University Press.

Collopy, P.D., Colot, H.V., Park, G., Ringelberg, C., Crew, C.M., Borkovich, K.A., Dunlap, J.C., 2010. High-throughput construction of gene deletion cassettes for generation of *Neurospora crassa* knockout strains. In: Methods in Molecular Biology, pp. 33–40.

Colot, H.V., Park, G., Turner, G.E., Ringelberg, C., Crew, C.M., Litvinkova, L., Weiss, R.L., Borkovich, K.A., Dunlap, J.C., 2006. A high-throughput gene knockout procedure for *Neurospora* reveals functions for multiple transcription factors. Proc. Natl. Acad. Sci. USA 103, 10352–10357.

Cooper, N., Thomas, G.H., Venditti, C., Meade, A., Freckleton, R.P., 2015. A cautionary note on the use of Ornstein Uhlenbeck models in macroevolutionary studies. Biol. J. Linn. Soc. Lond. 118, 64–77.

Costanzo, M., VanderSluis, B., Koch, E.N., Baryshnikova, A., Pons, C., Tan, G., Wang, W., Usaj, M., Hanchard, J., Lee, S.D., Pelechano, V., Styles, E.B., Billmann, M., van Leeuwen, J., van Dyk, N., Lin, Z.-Y., Kuzmin, E., Nelson, J., Piotrowski, J.S., Srikumar, T., Bahr, S., Chen, Y., Deshpande, R., Kurat, C.F., Li, S.C., Li, Z., Usaj, M.M., Okada, H., Pascoe, N., San Luis, B.-J., Sharifpoor, S., Shuteriqi, E., Simpkins, S.W., Snider, J., Suresh, H.G., Tan, Y., Zhu, H., Malod-Dognin, N., Janjic, V., Przulj, N., Troyanskaya, O.G., Stagljar, I., Xia, T., Ohya, Y., Gingras, A.-C., Raught, B., Boutros, M., Steinmetz, L.M., Moore, C.L., Rosebrock, A.P., Caudy, A.A., Myers, C.L., Andrews, B., Boone, C., 2016. A global genetic interaction network maps a wiring diagram of cellular function. Science 353. https://doi.org/10.1126/science.aaf1420.

Cracraft, J., 2005. Phylogeny and evo-devo: characters, homology, and the historical analysis of the evolution of development. Zoology 108, 345–356.

Croft, J.H., 1966. A reciprocal phenotypic instability affecting development in *Aspergillus nidulans*. Heredity 21, 565–579.
Cuomo, C.A., Güldener, U., Xu, J.-R., Trail, F., Turgeon, B.G., Di Pietro, A., Walton, J.D., Ma, L.-J., Baker, S.E., Rep, M., Adam, G., Antoniw, J., Baldwin, T., Calvo, S., Chang, Y.-L., Decaprio, D., Gale, L.R., Gnerre, S., Goswami, R.S., Hammond-Kosack, K., Harris, L.J., Hilburn, K., Kennell, J.C., Kroken, S., Magnuson, J.K., Mannhaupt, G., Mauceli, E., Mewes, H.-W., Mitterbauer, R., Muehlbauer, G., Münsterkötter, M., Nelson, D., O'donnell, K., Ouellet, T., Qi, W., Quesneville, H., Roncero, M.I.G., Seong, K.-Y., Tetko, I.V., Urban, M., Waalwijk, C., Ward, T.J., Yao, J., Birren, B.W., Kistler, H.C., 2007. The *Fusarium graminearum* genome reveals a link between localized polymorphism and pathogen specialization. Science 317, 1400–1402.
Dai, Y.-C., Cui, B.-K., 2011. *Fomitiporia ellipsoidea* has the largest fruiting body among the fungi. Fungal Biol. 115, 813–814.
Dasgupta, A., Chen, C.-H., Lee, C., Gladfelter, A.S., Dunlap, J.C., Loros, J.J., 2015. Biological significance of photoreceptor photocycle length: VIVID photocycle governs the dynamic VIVID-White collar complex pool mediating photo-adaptation and response to changes in light intensity. PLoS Genet. 11, e1005215.
Davis, R.H., 2000. *Neurospora*: Contributions of a Model Organism. Oxford University Press.
Davis, R.H., Perkins, D.D., 2002. Timeline: *Neurospora*: a model of model microbes. Nat. Rev. Genet. 3, 397–403.
Dean, R.A., Talbot, N.J., Ebbole, D.J., Farman, M.L., Mitchell, T.K., Orbach, M.J., Thon, M., Kulkarni, R., Xu, J.-R., Pan, H., Read, N.D., Lee, Y.-H., Carbone, I., Brown, D., Oh, Y.Y., Donofrio, N., Jeong, J.S., Soanes, D.M., Djonovic, S., Kolomiets, E., Rehmeyer, C., Li, W., Harding, M., Kim, S., Lebrun, M.-H., Bohnert, H., Coughlan, S., Butler, J., Calvo, S., Ma, L.-J., Nicol, R., Purcell, S., Nusbaum, C., Galagan, J.E., Birren, B.W., 2005. The genome sequence of the rice blast fungus *Magnaporthe grisea*. Nature 434, 980–986.
de Luis Balaguer, M.A., Sozzani, R., 2017. Inferring gene regulatory networks in the *Arabidopsis* root using a dynamic Bayesian network approach. Meth. Mol. Biol. 1629, 331–348.
Demidenko, N.V., Penin, A.A., 2012. Comparative analysis of gene expression level by quantitative real-time PCR has limited application in objects with different morphology. PLoS One 7e38161.
DeRisi, J.L., Iyer, V.R., Brown, P.O., 1997. Exploring the metabolic and genetic control of gene expression on a genomic scale. Science 278, 680–686.
Díaz, H., Andrews, B.A., Hayes, A., Castrillo, J., Oliver, S.G., Asenjo, J.A., 2009. Global gene expression in recombinant and non-recombinant yeast *Saccharomyces cerevisiae* in three different metabolic states. Biotechnol. Adv. 27, 1092–1117.
Diepeveen, E.T., Pourquie, V., Gehrmann, T., Abeel, T., Laan, L., 2017. Patterns of Conservation and Diversification in the Fungal Polarization Network. https://doi.org/10.1101/154641.
Dong, W., Tang, X., Yu, Y., Nilsen, R., Kim, R., Griffith, J., Arnold, J., Schüttler, H.-B., 2008. Systems biology of the clock in *Neurospora crassa*. PLoS One 3 e3105.
Dornburg, A., Townsend, J.P., Wang, Z., 2017. Maximizing power in phylogenetics and phylogenomics: a perspective illuminated by fungal big data. Adv. Genet. 100, 1–47.
Drews, G., 2001. The developmental biology of fungi—A new concept introduced by Anton de Bary. In: Advances in Applied Microbiology, pp. 213–227.
Drost, H.-G., Gabel, A., Grosse, I., Quint, M., 2015. Evidence for active maintenance of phylotranscriptomic hourglass patterns in animal and plant embryogenesis. Mol. Biol. Evol. 32, 1221–1231.
Drubin, D.G., 1991. Development of cell polarity in budding yeast. Cell 65, 1093–1096.
Dunlap, J.C., 2008. Salad days in the rhythms trade. Genetics 178, 1–13.
Dunlap, J.C., Borkovich, K.A., Henn, M.R., Turner, G.E., Sachs, M.S., Glass, N.L., McCluskey, K., Plamann, M., Galagan, J.E., Birren, B.W., Weiss, R.L., Townsend, J.P., Loros, J.J., Nelson, M.A., Lambreghts, R., Colot, H.V., Park, G., Collopy, P., Ringelberg, C., Crew, C., Litvinkova, L., DeCaprio, D., Hood, H.M., Curilla, S., Shi, M., Crawford, M., Koerhsen, M., Montgomery, P., Larson, L., Pearson, M., Kasuga, T., Tian, C., Baştürkmen, M., Altamirano, L., Xu, J., 2007. Enabling a community to dissect an organism: overview of the *Neurospora* functional genomics project. Adv. Genet. 57, 49–96.
Dunlap, J.C., Loros, J.J., Colot, H.V., Mehra, A., Belden, W.J., Shi, M., Hong, C.I., Larrondo, L.F., Baker, C.L., Chen, C.-H., Schwerdtfeger, C., Collopy, P.D., Gamsby, J.J., Lambreghts, R., 2007. A circadian clock in *Neurospora*: how genes and proteins cooperate to produce a sustained, entrainable, and compensated biological oscillator with a period of about a day. Cold Spring Harbor Symp. Quant. Biol. 72, 57–68.
Egel, R., 2013. The Molecular Biology of *Schizosaccharomyces pombe*: Genetics, Genomics and Beyond. Springer Science & Business Media.
Emmert-Streib, F., Glazko, G.V., 2011. Pathway analysis of expression data: deciphering functional building blocks of complex diseases. PLoS Comput. Biol. 7 e1002053.
Ene, I.V., Lohse, M.B., Vladu, A.V., Morschhäuser, J., Johnson, A.D., Bennett, R.J., 2016. Phenotypic profiling reveals that *Candida albicans* opaque cells represent a metabolically specialized cell state compared to default white cells. mBio 7. https://doi.org/10.1128/mBio.01269-16.
Engh, I., Nowrousian, M., Kück, U., 2010. *Sordaria macrospora*, a model organism to study fungal cellular development. Eur. J. Cell Biol. 89, 864–872.
Esser, K., Lemke, P.A., 1994. The Mycota: Growth, Differentiation, and Sexuality. Springer.
Essig, F.M., 1922. The Morphology, Development, and Economic Aspects of *Schizophyllum Commune* Fries.
Floudas, D., Binder, M., Riley, R., Barry, K., Blanchette, R.A., Henrissat, B., Martínez, A.T., Otillar, R., Spatafora, J.W., Yadav, J.S., Aerts, A., Benoit, I., Boyd, A., Carlson, A., Copeland, A., Coutinho, P.M., de Vries, R.P., Ferreira, P., Findley, K., Foster, B., Gaskell, J., Glotzer, D., Górecki, P., Heitman, J., Hesse, C., Hori, C., Igarashi, K., Jurgens, J.A., Kallen, N., Kersten, P., Kohler, A., Kües, U., Kumar, T.K.A., Kuo, A., LaButti, K., Larrondo, L.F., Lindquist, E., Ling, A., Lombard, V., Lucas, S., Lundell, T., Martin, R., McLaughlin, D.J., Morgenstern, I., Morin, E., Murat, C., Nagy, L.G., Nolan, M., Ohm, R.A., Patyshakuliyeva, A., Rokas, A., Ruiz-Dueñas, F.J., Sabat, G., Salamov, A., Samejima, M., Schmutz, J., Slot, J.C., St John, F., Stenlid, J., Sun, H., Sun, S., Syed, K., Tsang, A., Wiebenga, A., Young, D., Pisabarro, A., Eastwood, D.C., Martin, F., Cullen, D., Grigoriev, I.V., Hibbett, D.S., 2012. The Paleozoic origin of enzymatic lignin decomposition reconstructed from 31 fungal genomes. Science 336, 1715–1719.
Freeman, T.C., Ivens, A., Baillie, J.K., Beraldi, D., Barnett, M.W., Dorward, D., Downing, A., Fairbairn, L., Kapetanovic, R., Raza, S., Tomoiu, A., Alberio, R., Wu, C., Su, A.I., Summers, K.M., Tuggle, C.K., Archibald, A.L., Hume, D.A., 2012. A gene expression atlas of the domestic pig. BMC Biol. 10, 90.
Fuchs, S.M., Quasem, I., 2014. Budding yeast as a model to study epigenetics. Drug Discov. Today Dis. Model. 12, 1–6.
Fu, C., Iyer, P., Herkal, A., Abdullah, J., Stout, A., Free, S.J., 2011. Identification and characterization of genes required for cell-to-cell fusion in *Neurospora crassa*. Eukaryot. Cell 10, 1100–1109.
Fu, C., Tanaka, A., Free, S.J., 2014. *Neurospora crassa* 1,3-glucan synthase, AGS-1, is required for cell wall biosynthesis during macroconidia development. Microbiology 160, 1618–1627.

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

Fu, Y., Dai, Y., Yang, C., Wei, P., Song, B., Yang, Y., Sun, L., Zhang, Z.-W., Li, Y., 2017. Comparative transcriptome analysis identified candidate genes related to Bailinggu mushroom formation and genetic markers for genetic analyses and breeding. Sci. Rep. 7, 9266.

Galagan, J.E., Calvo, S.E., Borkovich, K.A., Selker, E.U., Read, N.D., Jaffe, D., FitzHugh, W., Ma, L.-J., Smirnov, S., Purcell, S., Rehman, B., Elkins, T., Engels, R., Wang, S., Nielsen, C.B., Butler, J., Endrizzi, M., Qui, D., Ianakiev, P., Bell-Pedersen, D., Nelson, M.A., Werner-Washburne, M., Selitrennikoff, C.P., Kinsey, J.A., Braun, E.L., Zelter, A., Schulte, U., Kothe, G.O., Jedd, G., Mewes, W., Staben, C., Marcotte, E., Greenberg, D., Roy, A., Foley, K., Naylor, J., Stange-Thomann, N., Barrett, R., Gnerre, S., Kamal, M., Kamvysselis, M., Mauceli, E., Bielke, C., Rudd, S., Frishman, D., Krystofova, S., Rasmussen, C., Metzenberg, R.L., Perkins, D.D., Kroken, S., Cogoni, C., Macino, G., Catcheside, D., Li, W., Pratt, R.J., Osmani, S.A., DeSouza, C.P.C., Glass, L., Orbach, M.J., Berglund, J.A., Voelker, R., Yarden, O., Plamann, M., Seiler, S., Dunlap, J., Radford, A., Aramayo, R., Natvig, D.O., Alex, L.A., Mannhaupt, G., Ebbole, D.J., Freitag, M., Paulsen, I., Sachs, M.S., Lander, E.S., Nusbaum, C., Birren, B., 2003. The genome sequence of the filamentous fungus *Neurospora crassa*. Nature 422, 859–868.

Galagan, J.E., Calvo, S.E., Cuomo, C., Ma, L.-J., Wortman, J.R., Batzoglou, S., Lee, S.-I., Baştürkmen, M., Spevak, C.C., Clutterbuck, J., Kapitonov, V., Jurka, J., Scazzocchio, C., Farman, M., Butler, J., Purcell, S., Harris, S., Braus, G.H., Draht, O., Busch, S., D'Enfert, C., Bouchier, C., Goldman, G.H., Bell-Pedersen, D., Griffiths-Jones, S., Doonan, J.H., Yu, J., Vienken, K., Pain, A., Freitag, M., Selker, E.U., Archer, D.B., Peñalva, M.A., Oakley, B.R., Momany, M., Tanaka, T., Kumagai, T., Asai, K., Machida, M., Nierman, W.C., Denning, D.W., Caddick, M., Hynes, M., Paoletti, M., Fischer, R., Miller, B., Dyer, P., Sachs, M.S., Osmani, S.A., Birren, B.W., 2005. Sequencing of *Aspergillus nidulans* and comparative analysis with *A. fumigatus* and *A. oryzae*. Nature 438, 1105–1115.

Gan, P., Ikeda, K., Irieda, H., Narusaka, M., O'Connell, R.J., Narusaka, Y., Takano, Y., Kubo, Y., Shirasu, K., 2012. Comparative genomic and transcriptomic analyses reveal the hemibiotrophic stage shift of *Colletotrichum* fungi. New Phytol. 197, 1236–1249.

Garzia, A., Etxebeste, O., Rodríguez-Romero, J., Fischer, R., Espeso, E.A., Ugalde, U., 2013. Transcriptional changes in the transition from vegetative cells to asexual development in the model fungus *Aspergillus nidulans*. Eukaryot. Cell 12, 311–321.

Geoghegan, I., Steinberg, G., Gurr, S., 2017. The role of the fungal cell wall in the infection of plants. Trends Microbiol. https://doi.org/10.1016/j.tim.2017.05.015.

Ge, Y., Wang, Y., Liu, Y., Tan, Y., Ren, X., Zhang, X., Hyde, K.D., Liu, Y., Liu, Z., 2016. Comparative genomic and transcriptomic analyses of the Fuzhuan brick tea-fermentation fungus *Aspergillus cristatus*. BMC Genom. 17, 428.

Ghanmi, N., Ali, M., Essoukri, N., 2011. Characterization of dynamic Bayesian network-the dynamic Bayesian network as temporal network. Int. J. Adv. Comput. Sci. Appl. 2. https://doi.org/10.14569/ijacsa.2011.020708.

Glassman, S.I., Levine, C.R., DiRocco, A.M., Battles, J.J., Bruns, T.D., 2016. Ectomycorrhizal fungal spore bank recovery after a severe forest fire: some like it hot. ISME J. 10, 1228–1239.

Guo, Z., Adomas, A.B., Jackson, E.D., Qin, H., Townsend, J.P., 2011. SIR2 and other genes are abundantly expressed in long-lived natural segregants for replicative aging of the budding yeast *Saccharomyces cerevisiae*. FEMS Yeast Res. 11, 345–355.

Guthke, R., Gerber, S., Conrad, T., Vlaic, S., Durmuş, S., Çakır, T., Sevilgen, F.E., Shelest, E., Linde, J., 2016. Data-based reconstruction of gene regulatory networks of fungal pathogens. Front. Microbiol. 7. https://doi.org/10.3389/fmicb.2016.00570.

Hall, B.K., 2012. Evolutionary developmental biology (evo-devo): past, present, and future. Evol. Educ. Outreach 5, 184–193.

Hecker, M., Lambeck, S., Toepfer, S., van Someren, E., Guthke, R., 2009. Gene regulatory network inference: data integration in dynamic models-a review. Biosystems 96, 86–103.

He, H., Lin, D., Zhang, J., Wang, Y.-P., Deng, H.-W., 2017. Comparison of statistical methods for subnetwork detection in the integration of gene expression and protein interaction network. BMC Bioinf. 18, 149.

Heitman, J., 2015. Evolution of sexual reproduction: a view from the fungal kingdom supports an evolutionary epoch with sex before sexes. Fungal Biol. Rev. 29, 108–117.

Hibbett, D.S., Donoghue, M.J., 2001. Analysis of character correlations among wood decay mechanisms, mating systems, and substrate ranges in homobasidiomycetes. Syst. Biol. 50, 215–242.

Honda, S., Bicocca, V.T., Gessaman, J.D., Rountree, M.R., Yokoyama, A., Yu, E.Y., Selker, J.M.L., Selker, E.U., 2016. Dual chromatin recognition by the histone deacetylase complex HCHC is required for proper DNA methylation in *Neurospora crassa*. Proc. Natl. Acad. Sci. USA 113, E6135–E6144.

Hong, C.I., Zámborszky, J., Baek, M., Labiscsak, L., Ju, K., Lee, H., Larrondo, L.F., Goity, A., Chong, H.S., Belden, W.J., Csikász-Nagy, A., 2014. Circadian rhythms synchronize mitosis in *Neurospora crassa*. Proc. Natl. Acad. Sci. USA 111, 1397–1402.

Huang, T., López-Giráldez, F., Townsend, J.P., Irish, V.F., 2012. RBE controls microRNA164 expression to effect floral organogenesis. Development 139, 2161–2169.

Hyde, K.D., Swe, A., Zhang, K.-Q., 2014. Nematode-trapping fungi. In: Fungal Diversity Research Series, pp. 1–12.

Ideker, T., Thorsson, V., Ranish, J.A., Christmas, R., Buhler, J., Eng, J.K., Bumgarner, R., Goodlett, D.R., Aebersold, R., Hood, L., 2001. Integrated genomic and proteomic analyses of a systematically perturbed metabolic network. Science 292, 929–934.

Iwaniuk, A., Błaszkowski, J., 2014. Arbuscular fungi and mycorrhizae of agricultural soils of the Western Pomerania. Part I. Occurrence of arbuscular fungi and mycorrhizae. Acta Mycol. 39, 65–91.

Iyer, S.V., Ramakrishnan, M., Kasbekar, D.P., 2009. *Neurospora crassa* fmf-1 encodes the homologue of the *Schizosaccharomyces pombe* Ste11p regulator of sexual development. J. Genet. 88, 33–39.

Jiang, Y., Wang, W., Xie, Q., Liu, N., Liu, L., Wang, D., Zhang, X., Yang, C., Chen, X., Tang, D., Wang, E., 2017. Plants transfer lipids to sustain colonization by mutualistic mycorrhizal and parasitic fungi. Science 356, 1172–1175.

Joy, J.B., Liang, R.H., McCloskey, R.M., Nguyen, T., Poon, A.F.Y., 2016. Ancestral reconstruction. PLoS Comput. Biol. 12, e1004763.

Judge, M., Griffith, J., Arnold, J., 2017. Aging and the biological clock. In: Healthy Ageing and Longevity, pp. 211–234.

Junjie-Yuan, Junjie-Yuan, Pingping-Li, Yongguang-Hu, 2010. Study in dynamic growth model of *Coprinus Comatus* based on temperature and humidity. In: The 2nd International Conference on Information Science and Engineering. https://doi.org/10.1109/icise.2010.5691021.

Kalinka, A.T., Varga, K.M., Gerrard, D.T., Preibisch, S., Corcoran, D.L., Jarrells, J., Ohler, U., Bergman, C.M., Tomancak, P., 2010. Gene expression divergence recapitulates the developmental hourglass model. Nature 468, 811–814.

Kaneko, K., 2006. Life: an Introduction to Complex Systems Biology. Springer.

Keller, N., 2006. *Aspergillus nidulans*: a model for elucidation of *Aspergillus fumigatus* secondary metabolism. In: Molecular Principles of Fungal Pathogenesis, pp. 235–243.
Keller, N.P., Turner, G., Bennett, J.W., 2005. Fungal secondary metabolism — from biochemistry to genomics. Nat. Rev. Microbiol. 3, 937–947.
Kim, S., Imoto, S., Miyano, S., 2004. Dynamic Bayesian network and nonparametric regression for nonlinear modeling of gene networks from time series gene expression data. Biosystems 75, 57–65.
Knaack, S.A., Thompson, D.A., Roy, S., 2016. Reconstruction and analysis of the evolution of modular transcriptional regulatory programs using arboretum. In: Methods in Molecular Biology, pp. 375–389.
Kopke, K., Hoff, B., Kück, U., 2010. Application of the *Saccharomyces cerevisiae* FLP/FRT recombination system in filamentous fungi for marker recycling and construction of knockout strains devoid of heterologous genes. Appl. Environ. Microbiol. 76, 4664–4674.
Kronholm, I., Johannesson, H., Ketola, T., 2016. Epigenetic control of phenotypic plasticity in the filamentous fungus *Neurospora crassa*. G3 6, 4009–4022.
Krystofova, S., Borkovich, K.A., 2006. The predicted G-protein-coupled receptor GPR-1 is required for female sexual development in the multicellular fungus *Neurospora crassa*. Eukaryot. Cell 5, 1503–1516.
Kück, U., 2013. Genetics and Biotechnology. Springer Science & Business Media.
Kües, U., Fischer, R., 2006. Growth, Differentiation and Sexuality. Springer Science & Business Media.
Lachance, M.-A., Perri, A.M., Farahbakhsh, A.S., Starmer, W.T., 2013. Genetic structure of *Kurtzmaniella cleridarum*, a cactus flower beetle yeast of the Sonoran and Mojave Deserts: speciation by distance? FEMS Yeast Res. 13, 674–681.
Lashkari, D.A., DeRisi, J.L., McCusker, J.H., Namath, A.F., Gentile, C., Hwang, S.Y., Brown, P.O., Davis, R.W., 1997. Yeast microarrays for genome wide parallel genetic and gene expression analysis. Proc. Natl. Acad. Sci. USA 94, 13057–13062.
Lehr, N.A., Wang, Z., Li, N., Hewitt, D.A., López-Giráldez, F., Trail, F., Townsend, J.P., 2014. Gene expression differences among three *Neurospora* species reveal genes required for sexual reproduction in *Neurospora crassa*. PLoS One 9, e110398.
Le Nagard, H., Chao, L., Tenaillon, O., 2011. The emergence of complexity and restricted pleiotropy in adapting networks. BMC Evol. Biol. 11, 326.
Li, H., Johnson, A.D., 2010. Evolution of transcription networks — lessons from yeasts. Curr. Biol. 20, R746–R753.
Lind, A., Lim, F.Y., Soukup, A., Keller, N., Rokas, A., 2017. A LaeA- and BrlA-dependent Cellular Network Governs Tissue-specific Secondary Metabolism in the Human Pathogen *Aspergillus fumigatus*. bioRxiv. https://doi.org/10.1101/196600.
Liti, G., 2014. Budding topics: insights from emerging scientists. Yeast 31, 195–195.
Li, Z., Li, P., Krishnan, A., Liu, J., 2011. Large-scale dynamic gene regulatory network inference combining differential equation models with local dynamic Bayesian network analysis. Bioinformatics 27, 2686–2691.
López-Kleine, L., Leal, L., López, C., 2013. Biostatistical approaches for the reconstruction of gene co-expression networks based on transcriptomic data. Brief. Funct. Genom. 12, 457–467.
Lord, K.M., Read, N.D., 2011. Perithecium morphogenesis in *Sordaria macrospora*. Fungal Genet. Biol. 48, 388–399.
Lu, M.-Y.J., Fan, W.-L., Wang, W.-F., Chen, T., Tang, Y.-C., Chu, F.-H., Chang, T.-T., Wang, S.-Y., Li, M.-Y., Chen, Y.-H., Lin, Z.-S., Yang, K.-J., Chen, S.-M., Teng, Y.-C., Lin, Y.-L., Shaw, J.-F., Wang, T.-F., Li, W.-H., 2014. Genomic and transcriptomic analyses of the medicinal fungus *Antrodia cinnamomea* for its metabolite biosynthesis and sexual development. Proc. Natl. Acad. Sci. USA 111, E4743–E4752.
Machida, M., Asai, K., Sano, M., Tanaka, T., Kumagai, T., Terai, G., Kusumoto, K.-I., Arima, T., Akita, O., Kashiwagi, Y., Abe, K., Gomi, K., Horiuchi, H., Kitamoto, K., Kobayashi, T., Takeuchi, M., Denning, D.W., Galagan, J.E., Nierman, W.C., Yu, J., Archer, D.B., Bennett, J.W., Bhatnagar, D., Cleveland, T.E., Fedorova, N.D., Gotoh, O., Horikawa, H., Hosoyama, A., Ichinomiya, M., Igarashi, R., Iwashita, K., Juvvadi, P.R., Kato, M., Kato, Y., Kin, T., Kokubun, A., Maeda, H., Maeyama, N., Maruyama, J.-I., Nagasaki, H., Nakajima, T., Oda, K., Okada, K., Paulsen, I., Sakamoto, K., Sawano, T., Takahashi, M., Takase, K., Terabayashi, Y., Wortman, J.R., Yamada, O., Yamagata, Y., Anazawa, H., Hata, Y., Koide, Y., Komori, T., Koyama, Y., Minetoki, T., Suharnan, S., Tanaka, A., Isono, K., Kuhara, S., Ogasawara, N., Kikuchi, H., 2005. Genome sequencing and analysis of *Aspergillus oryzae*. Nature 438, 1157–1161.
Macía, J., Solé, R.V., Elena, S.F., 2011. The causes of epistasis in genetic networks. Evolution 66, 586–596.
Maheshwari, R., 2016. Fungi: Experimental Methods. In: Biology, Second ed. CRC Press.
Marcum, J.A., 2009. The Conceptual Foundations of Systems Biology: an Introduction.
Marks, G.C., 2012. Ectomycorrhizae: Their Ecology and Physiology. Elsevier.
McCarthy, C.G.P., Fitzpatrick, D.A., 2017. Multiple approaches to phylogenomic reconstruction of the fungal kingdom. Adv. Genet. 100, 211–266.
McCluskey, K., Plamann, M., 2008. Perspectives on genetic resources at the Fungal Genetics Stock Center. Fungal Genet. Rep 55, 15–17.
McCluskey, K., Wiest, A.E., Grigoriev, I.V., Lipzen, A., Martin, J., Schackwitz, W., Baker, S.E., 2011. Rediscovery by whole genome sequencing: classical mutations and genome polymorphisms in *Neurospora crassa*. G3 1, 303–316.
Meinhardt, F., Wessels, J.G.H., 2013. Growth, Differentiation and Sexuality. Springer Science & Business Media.
Mendgen, K., Hahn, M., Deising, H., 1996. Morphogenesis and mechanisms of penetration by plant pathogenic fungi. Annu. Rev. Phytopathol. 34, 367–386.
Mitchell, M.B., 1955. Aberrant recombination of pyridoxine mutants of *Neurospora*. Proc. Natl. Acad. Sci. USA 41, 215–220.
Mohanta, T.K., Bae, H., 2015. The diversity of fungal genome. Biol. Proced. Online 17. https://doi.org/10.1186/s12575-015-0020-z.
Montenegro-Montero, A., Canessa, P., Larrondo, L.F., 2015. Around the fungal clock: recent advances in the molecular study of circadian clocks in *Neurospora* and other fungi. Adv. Genet. 92, 107–184.
Mustacchi, R., Hohmann, S., Nielsen, J., 2006. Yeast systems biology to unravel the network of life. Yeast 23, 227–238.
Nagy, L.G., Ohm, R.A., Kovács, G.M., Floudas, D., Riley, R., Gácser, A., Sipiczki, M., Davis, J.M., Doty, S.L., de Hoog, G.S., Lang, B.F., Spatafora, J.W., Martin, F.M., Grigoriev, I.V., Hibbett, D.S., 2014. Latent homology and convergent regulatory evolution underlies the repeated emergence of yeasts. Nat. Commun. 5, 4471.
Nagy, L.G., Riley, R., Bergmann, P.J., Krizsán, K., Martin, F.M., Grigoriev, I.V., Cullen, D., Hibbett, D.S., 2016. Genetic bases of fungal white rot wood decay predicted by phylogenomic analysis of correlated gene-phenotype evolution. Mol. Biol. Evol. 34, 35–44.
Nagy, L.G., Szöllősi, G., 2017. Fungal phylogeny in the age of genomics: insights into phylogenetic inference from genome-scale datasets. Adv. Genet. 100, 49–72.
Needham, C.J., Bradford, J.R., Bulpitt, A.J., Westhead, D.R., 2007. A primer on learning in Bayesian networks for computational biology. PLoS Comput. Biol. 3 e129.

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

Needham, C.J., Bradford, J.R., Bulpitt, A.J., Westhead, D.R., 2006. Inference in Bayesian networks. Nat. Biotechnol. 24, 51–53.
Ness, R.O., Sachs, K., Mallick, P., Vitek, O., 2017. A Bayesian active learning experimental design for inferring signaling networks. In: Lecture Notes in Computer Science, pp. 134–156.
Nierman, W.C., Pain, A., Anderson, M.J., Wortman, J.R., Kim, H.S., Arroyo, J., Berriman, M., Abe, K., Archer, D.B., Bermejo, C., Bennett, J., Bowyer, P., Chen, D., Collins, M., Coulsen, R., Davies, R., Dyer, P.S., Farman, M., Fedorova, N., Fedorova, N., Feldblyum, T.V., Fischer, R., Fosker, N., Fraser, A., García, J.L., García, M.J., Goble, A., Goldman, G.H., Gomi, K., Griffith-Jones, S., Gwilliam, R., Haas, B., Haas, H., Harris, D., Horiuchi, H., Huang, J., Humphray, S., Jiménez, J., Keller, N., Khouri, H., Kitamoto, K., Kobayashi, T., Konzack, S., Kulkarni, R., Kumagai, T., Lafon, A., Lafton, A., Latgé, J.-P., Li, W., Lord, A., Lu, C., Majoros, W.H., May, G.S., Miller, B.L., Mohamoud, Y., Molina, M., Monod, M., Mouyna, I., Mulligan, S., Murphy, L., O'Neil, S., Paulsen, I., Peñalva, M.A., Pertea, M., Price, C., Pritchard, B.L., Quail, M.A., Rabbinowitsch, E., Rawlins, N., Rajandream, M.-A., Reichard, U., Renauld, H., Robson, G.D., Rodriguez de Córdoba, S., Rodríguez-Peña, J.M., Ronning, C.M., Rutter, S., Salzberg, S.L., Sanchez, M., Sánchez-Ferrero, J.C., Saunders, D., Seeger, K., Squares, R., Squares, S., Takeuchi, M., Tekaia, F., Turner, G., Vazquez de Aldana, C.R., Weidman, J., White, O., Woodward, J., Yu, J.-H., Fraser, C., Galagan, J.E., Asai, K., Machida, M., Hall, N., Barrell, B., Denning, D.W., 2005. Genomic sequence of the pathogenic and allergenic filamentous fungus *Aspergillus fumigatus*. Nature 438, 1151–1156.
Ninova, M., Ronshaugen, M., Griffiths-Jones, S., 2014. Conserved temporal patterns of microRNA expression in *Drosophila* support a developmental hourglass model. Genom. Biol. Evol. 6, 2459–2467.
Nowrousian, M., 2014. 7 Genomics and transcriptomics to analyze fruiting body development. In: Fungal Genomics, pp. 149–172.
Nowrousian, M., Cebula, P., 2005. The gene for a lectin-like protein is transcriptionally activated during sexual development, but is not essential for fruiting body formation in the filamentous fungus *Sordaria macrospora*. BMC Microbiol. 5, 64.
Oguz, C., Watson, L.T., Baumann, W.T., Tyson, J.J., 2017. Predicting network modules of cell cycle regulators using relative protein abundance statistics. BMC Syst. Biol. 11, 30.
Osiewacz, H.D., 2002. Molecular Biology of Fungal Development. CRC Press.
Paradis, E., 2011. Analysis of Phylogenetics and Evolution with R. Springer Science & Business Media.
Paradis, E., Claude, J., Strimmer, K., 2004. APE: analyses of phylogenetics and evolution in R language. Bioinformatics 20, 289–290.
Park, C., Yun, S.J., Ryu, S.J., Lee, S., Lee, Y.-S., Yoon, Y., Park, S.C., 2017. Systematic identification of an integrative network module during senescence from time-series gene expression. BMC Syst. Biol. 11, 36.
Pauwels, E., Lajaunie, C., Vert, J.-P., 2014. A Bayesian active learning strategy for sequential experimental design in systems biology. BMC Syst. Biol. 8, 102.
Payne, J.L., Wagner, A., 2014. Latent phenotypes pervade gene regulatory circuits. BMC Syst. Biol. 8, 64.
Perrimon, N., Barkai, N., 2011. The era of systems developmental biology. Curr. Opin. Genet. Dev. 21, 681–683.
Picelli, S., 2017. Single-cell RNA-sequencing: the future of genome biology is now. RNA Biol. 14, 637–650.
Plaza, D., Lin, C.-W., van der Velden, N.S., Aebi, M., Künzler, M., 2014. Comparative transcriptomics of the model mushroom *Coprinopsis cinerea* reveals tissue-specific armories and a conserved circuitry for sexual development. BMC Genom. 15, 492.
Pöggeler, S., 2011. 5 Function and evolution of pheromones and pheromone receptors in Filamentous ascomycetes. In: Evolution of Fungi and Fungal-Like Organisms, pp. 73–96.
Prasad, R., 2017. *Candida albicans*: Cellular and Molecular Biology. Springer.
Quint, M., Drost, H.-G., Gabel, A., Ullrich, K.K., Bönn, M., Grosse, I., 2012. A transcriptomic hourglass in plant embryogenesis. Nature 490, 98–101.
Riquelme, M., Martínez-Núñez, L., 2016. Hyphal ontogeny in *Neurospora crassa*: a model organism for all seasons. F1000Res. 5, 2801.
Roche, C.M., Loros, J.J., McCluskey, K., Glass, N.L., 2014. *Neurospora crassa*: looking back and looking forward at a model microbe. Am. J. Bot. 101, 2022–2035.
Rodriguez-Romero, J., Hedtke, M., Kastner, C., Müller, S., Fischer, R., 2010. Fungi, hidden in soil or up in the air: light makes a difference. Annu. Rev. Microbiol. 64, 585–610.
Rohlfs, R.V., Harrigan, P., Nielsen, R., 2013. Modeling gene expression evolution with an extended Ornstein–Uhlenbeck process accounting for within-species variation. Mol. Biol. Evol. 31, 201–211.
Rokas, A., 2013. Aspergillus. Curr. Biol. 23, R187–R188.
Ronning, C.M., Fedorova, N.D., Bowyer, P., Coulson, R., Goldman, G., Kim, H.S., Turner, G., Wortman, J.R., Yu, J., Anderson, M.J., Denning, D.W., Nierman, W.C., 2005. Genomics of *Aspergillus fumigatus*. Rev. Iberoam. Micol 22, 223–228.
Rose, A.H., 1981. *Saccharomyces cerevisiae* as a model eukaryote. In: Advances in Biotechnology, pp. 645–652.
Roy, S., Bhattacharyya, D.K., Kalita, J.K., 2014. Reconstruction of gene co-expression network from microarray data using local expression patterns. BMC Bioinf. 15 (Suppl. 7), S10.
Roy, S., Wapinski, I., Pfiffner, J., French, C., Socha, A., Konieczka, J., Habib, N., Kellis, M., Thompson, D., Regev, A., 2013. Arboretum: reconstruction and analysis of the evolutionary history of condition-specific transcriptional modules. Genome Res. 23, 1039–1050.
Ruibal, C., Platas, G., Bills, G.F., 2008. High diversity and morphological convergence among melanised fungi from rock formations in the central mountain system of Spain. Persoonia 21, 93–110.
Ruiz-Herrera, J., Ortiz-Castellanos, L., 2010. Analysis of the phylogenetic relationships and evolution of the cell walls from yeasts and fungi. FEMS Yeast Res. 10, 225–243.
Salehzadeh-Yazdi, A., Asgari, Y., Saboury, A.A., Masoudi-Nejad, A., 2014. Computational analysis of reciprocal association of metabolism and epigenetics in the budding yeast: a genome-scale metabolic model (GSMM) approach. PLoS One 9 e111686.
Schindler, D., Nowrousian, M., 2014. The polyketide synthase gene pks4 is essential for sexual development and regulates fruiting body morphology in *Sordaria macrospora*. Fungal Genet. Biol. 68, 48–59.
Schluter, D., Price, T., Mooers, A.Ø., Ludwig, D., 1997. Likelihood of ancerstor states in adaptive radiation. Evolution 51, 1699–1711.
Seibert, T., Thieme, N., Philipp Benz, J., 2016. The renaissance of *Neurospora crassa*: How a classical model system is used for applied research. In: Fungal Biology, pp. 59–96.
Selker, E.U., 2017. Neurospora crassa. In: Reference Module in Life Sciences.
Selker, E.U., 2011. Neurospora. Curr. Biol. 21, R139–R140.
Seo, J.-A., 2005. FluG-dependent asexual development in *Aspergillus nidulans* occurs via derepression. Genetics 172, 1535–1544.
Shamir, R., 2008. On the evolution of transcription regulation networks. In: Regulatory Genomics. https://doi.org/10.1142/9781848162525_0007.

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

Shang, Y., Xiao, G., Zheng, P., Cen, K., Zhan, S., Wang, C., 2016. Divergent and convergent evolution of fungal pathogenicity. Genome Biol. Evol. 8, 1374–1387.
Shestakova, E., 2015. Different mechanisms of epigenetic regulation of gene expression. MOJ Cell Sci. Rep. 2. https://doi.org/10.15406/mojcsr.2015.02.00019.
Sikhakolli, U.R., López-Giráldez, F., Li, N., Common, R., Townsend, J.P., Trail, F., 2012. Transcriptome analyses during fruiting body formation in *Fusarium graminearum* and *Fusarium verticillioides* reflect species life history and ecology. Fungal Genet. Biol. 49, 663–673.
Smith, M.L., Bruhn, J.N., Anderson, J.B., 1992. The fungus *Armillaria bulbosa* is among the largest and oldest living organisms. Nature 356, 428–431.
Springer, M.L., 1993. Genetic control of fungal differentiation: the three sporulation pathways of *Neurospora crassa*. Bioessays 15, 365–374.
Springer, M.L., Yanofsky, C., 1992. Expression of con genes along the three sporulation pathways of *Neurospora crassa*. Genes Dev. 6, 1052–1057.
Stajich, J., 2014. Faculty of 1000 evaluation for global gene expression and focused knockout analysis reveals genes associated with fungal fruiting body development in *Neurospora crassa*. In: F1000-Post-Publication Peer Review of the Biomedical Literature. https://doi.org/10.3410/f.718179404.793497630.
Stajich, J.E., Berbee, M.L., Blackwell, M., Hibbett, D.S., James, T.Y., Spatafora, J.W., Taylor, J.W., 2009. The fungi. Curr. Biol. 19, R840–R845.
Stefanini, I., Dapporto, L., Legras, J.-L., Calabretta, A., Di Paola, M., De Filippo, C., Viola, R., Capretti, P., Polsinelli, M., Turillazzi, S., Cavalieri, D., 2012. Role of social wasps in *Saccharomyces cerevisiae* ecology and evolution. Proc. Natl. Acad. Sci. USA 109, 13398–13403.
Taylor, J.W., Branco, S., Gao, C., Hann-Soden, C., Montoya, L., Sylvain, I., Gladieux, P., 2017. Sources of fungal genetic variation and associating It with phenotypic diversity. Microbiol. Spectr. 5. https://doi.org/10.1128/microbiolspec.FUNK-0057-2016.
Teichert, I., Lutomski, M., Märker, R., Nowrousian, M., Kück, U., 2016. New insights from an old mutant: SPADIX4 governs fruiting body development but not hyphal fusion in *Sordaria macrospora*. Mol. Genet. Genom. 292, 93–104.
Teichert, I., Nowrousian, M., Pöggeler, S., Kück, U., 2014. The filamentous fungus *Sordaria macrospora* as a genetic model to study fruiting body development. Adv. Genet. 87, 199–244.
Teichert, I., Wolff, G., Kück, U., Nowrousian, M., 2012. Combining laser microdissection and RNA-seq to chart the transcriptional landscape of fungal development. BMC Genom. 13, 511.
Tian, C., Beeson, W.T., Iavarone, A.T., Sun, J., Marletta, M.A., Cate, J.H.D., Glass, N.L., 2009. Systems analysis of plant cell wall degradation by the model filamentous fungus *Neurospora crassa*. Proc. Natl. Acad. Sci. USA 106, 22157–22162.
Timberlake, W.E., 1993. Translational triggering and feedback fixation in the control of fungal development. Plant Cell 5, 1453–1460.
Tomičić, R., Raspor, P., 2017. Influence of growth conditions on adhesion of yeast *Candida* spp. and *Pichia* spp. to stainless steel surfaces. Food Microbiol. 65, 179–184.
Tong, A.H.Y., 2004. Global mapping of the yeast genetic interaction network. Science 303, 808–813.
Tong, S., Koller, D., 2001. Active learning for structure in Bayesian networks. In: International Joint Conference on Artificial Intelligence. Lawrence Erlbaum Associates ltd, pp. 863–869.
Torruella, G., de Mendoza, A., Grau-Bové, X., Antó, M., Chaplin, M.A., del Campo, J., Eme, L., Pérez-Cordón, G., Whipps, C.M., Nichols, K.M., Paley, R., Roger, A.J., Sitjà-Bobadilla, A., Donachie, S., Ruiz-Trillo, I., 2015. Phylogenomics reveals convergent evolution of lifestyles in close relatives of animals and fungi. Curr. Biol. 25, 2404–2410.
Trail, F., 2013. Sex and fruiting in Fusarium. In: Brown, D.W., Proctor, R.H. (Eds), Fusarium: Genomics, Molecular and Cellular Biology. Horizon Scientific Press, pp. 12–28.
Trail, F., Wang, Z., Stefanko, K., Cubba, C., Townsend, J.P., 2017. The ancestral levels of transcription and the evolution of sexual phenotypes in filamentous fungi. PLoS Genet. 13, e1006867.
Tsubouchi, H., 2006. Budding yeast Hed1 down-regulates the mitotic recombination machinery when meiotic recombination is impaired. Genes Dev. 20, 1766–1775.
Vigfusson, N.V., Weijer, J., 1972. Sexuality in *Neurospora crassa* II. genes affecting the sexual development cycle. Genet. Res. 19, 205.
Wang, Z., Henrik Nilsson, R., James, T.Y., Dai, Y., Townsend, J.P., 2016. Future perspectives and challenges of fungal systematics in the age of big data. In: Fungal Biology, pp. 25–46.
Wang, Z., Johnston, P.R., Yang, Z.L., Townsend, J.P., 2009. Evolution of reproductive morphology in leaf endophytes. PLoS One 4, e4246.
Wang, Z., Kin, K., López-Giráldez, F., Johannesson, H., Townsend, J.P., 2012. Sex-specific gene expression during asexual development of *Neurospora crassa*. Fungal Genet. Biol. 49, 533–543.
Wang, Z., Lopez-Giraldez, F., Lehr, N., Farré, M., Common, R., Trail, F., Townsend, J.P., 2014. Global gene expression and focused knockout analysis reveals genes associated with fungal fruiting body development in *Neurospora crassa*. Eukaryot. Cell 13, 154–169.
Watters, M.K., Boersma, M., Johnson, M., Reyes, C., Westrick, E., Lindamood, E., 2011. A screen for *Neurospora* knockout mutants displaying growth rate dependent branch density. Fungal Biol. 115, 296–301.
Wendland, J., 2016. Growth, Differentiation and Sexuality. Springer.
Wessels, J.G.H., 1989. Molecular development of *Schizophyllum commune*. Cell Differ. Dev. 27, 8.
West-Eberhard, M.J., 2003. Developmental Plasticity and Evolution. Oxford University Press.
Whittle, C.A., Johannesson, H., 2011. 12 evolution of mating-type loci and mating-type chromosomes in model species of *Filamentous Ascomycetes*. In: Evolution of Fungi and Fungal-Like Organisms, pp. 277–292.
Winterboer, A., Eicker, A., 1983. A contribution to the basidiocarp morphology of *Coprinus comatus*. Suid-Afr. Tydskr. vir Natuurwetenskap Tegnol. 2. https://doi.org/10.4102/satnt.v2i3.1118.
Winters, C.M., Chiang, H.-L., 2016. Yeast as a model system to study trafficking of small vesicles carrying signal-less proteins in and out of the cell. Curr. Protein Pept. Sci. 17, 808–820.
Wu, G., Zhao, H., Li, C., Rajapakse, M.P., Wong, W.C., Xu, J., Saunders, C.W., Reeder, N.L., Reilman, R.A., Scheynius, A., Sun, S., Billmyre, B.R., Li, W., Averette, A.F., Mieczkowski, P., Heitman, J., Theelen, B., Schröder, M.S., De Sessions, P.F., Butler, G., Maurer-Stroh, S., Boekhout, T., Nagarajan, N., Dawson Jr., T.L., 2015. Genus-wide comparative genomics of *Malassezia* delineates its phylogeny, physiology, and niche adaptation on human skin. PLoS Genet. 11 e1005614.
Xie, X., Lipke, P.N., 2010. On the evolution of fungal and yeast cell walls. Yeast 27, 479–488.
Yin, C., Downey, S.I., Klages-Mundt, N.L., Ramachandran, S., Chen, X., Szabo, L.J., Pumphrey, M., Hulbert, S.H., 2015. Identification of promising host-induced silencing targets among genes preferentially transcribed in haustoria of *Puccinia*. BMC Genom. 16, 579.

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001

Yin, W.-B., Reinke, A.W., Szilágyi, M., Emri, T., Chiang, Y.-M., Keating, A.E., Pócsi, I., Wang, C.C.C., Keller, N.P., 2013. bZIP transcription factors affecting secondary metabolism, sexual development and stress responses in *Aspergillus nidulans*. Microbiology 159, 77–88.

Young, W.C., Raftery, A.E., Yeung, K.Y., 2014. Fast Bayesian inference for gene regulatory networks using Scan BMA. BMC Syst. Biol. 8, 47.

Yu, J., Cleveland, T.E., Nierman, W.C., Bennett, J.W., 2005. *Aspergillus flavus* genomics: gateway to human and animal health, food safety, and crop resistance to diseases. Rev. Iberoam. Micol 22, 194–202.

Zamanighomi, M., Zamanian, M., Kimber, M.J., Wang, Z., 2014. Gene Regulatory Network Inference from Perturbed Time-series Expression Data via Ordered Dynamical Expansion of Non-steady State Actors. https://doi.org/10.1101/007906.

Zarringhalam, K., Enayetallah, A., Gutteridge, A., Sidders, B., Ziemek, D., 2013. Molecular causes of transcriptional response: a Bayesian prior knowledge approach. Bioinformatics 29, 3167–3173.

Zeng, F., Lian, X., Zhang, G., Yu, X., Bradley, C.A., Ming, R., 2017. A comparative genome analysis of *Cercospora sojina* with other members of the pathogen genus *Mycosphaerella* on different plant hosts. Genom. Data 13, 54–63.

Zhang, J., Ren, A., Chen, H., Zhao, M., Shi, L., Chen, M., Wang, H., Feng, Z., 2015. Transcriptome analysis and its application in identifying genes associated with fruiting body development in basidiomycete *Hypsizygus marmoreus*. PLoS One 10 e0123025.

Zhang, N., Luo, J., Bhattacharya, D., 2017. Advances in fungal phylogenomics and their impact on fungal systematics. Adv. Genet. 100, 309–328.

Ziebarth, J.D., Bhattacharya, A., Cui, Y., 2013. Bayesian network webserver: a comprehensive tool for biological network modeling. Bioinformatics 29, 2801–2803.

Ziebarth, J.D., Cui, Y., 2016. Precise network modeling of systems genetics data using the Bayesian network webserver. In: Methods in Molecular Biology, pp. 319–335.

Please cite this article in press as: Wang, Z., et al., Using evolutionary genomics, transcriptomics, and systems biology to reveal gene networks underlying fungal development, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.02.001