Meeting report

The fungal frontier

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A report of the 24th Fungal Genetics Conference, Asilomar, USA, 20-25 March 2007.

Fungal biology has long provided mechanistic insight into the workings of all eukaryotes, and the growing number of sequenced fungal genomes - 56 and counting - is yielding unprecedented views of genome evolution and its sometimes surprising driving forces. New research is uncovering why pathogens are pathogenic, how fungi respond to their environment, what forces drive the divergence of related species, and what processes underlie this evolution. Never was this more apparent than at the fungal genetics conference in Asilomar this March.

Phylogeny and evolution of paralogs and gene families

The ancestor of *Saccharomyces cerevisiae* and closely related species underwent a whole-genome duplication event, followed by loss of most duplicated regions. Ken Wolfe's group (Trinity College, Dublin, Ireland) has found some surprises in the aftermath of the whole-genome duplication from the sequence of *Kluyveromyces polysporus*. The *K. polysporus* and *S. cerevisiae* genomes are similar in size, gene number and overall distribution of gene function, but the post-duplication loss events in each lineage are different: in numerous cases, *K. polysporus* retains the paralog of an *S. cerevisiae* gene. Interestingly, many genes remain duplicated in both species, suggesting a considerable selective advantage for their maintenance.

Functional relationships between paralogs that date back to the whole-genome duplication have begun to reveal mechanisms of subfunctionalization: how duplicated genes evolve distinct functions. Laura Rusche (Duke University, Durham, USA) has focused on the paralogous histone deacetylases Sir2 and Hst1 of *S. cerevisiae* that govern, respectively, subtelomeric silencing and silencing of dispersed sporulation genes. There is a single Sir2/Hst1 paralog in *K. lactis*, which diverged from *S. cerevisiae* before the whole-genome duplication, and this paralog can carry out both functions in *K. lactis* as well as when ectopically expressed in *S. cerevisiae*. Remarkably, *S. cerevisiae* Sir2 can also perform both functions, but only in the absence of Hst1, which otherwise excludes Sir2 from sporulation promoter regions. Hence, subfunctionalization is driven here by competition between paralogous proteins rather than by a pronounced loss of specific functional abilities.

Gene duplications are frequent even in phylogenies that have not undergone whole-genome duplication. At one extreme, there are families composed of tandem clusters of genes, and Jason Stajich (University of California, Berkeley, USA) reported on the results of phylogenetic analysis. The P450 gene family, whose members are critical for lignin breakdown, arose independently in *Phanerochaete chrysosporium* and *Coprinus cinereus*. Similar evidence supports independent evolution of protease families in *Coccidioides* and *Histoplasma*, and of the hydrophobins that promote production of airborne spores in many fungi. More common than large families of genes are pairs of paralogs, whose evolution has been examined by several groups through gene phylogenies of closely related species. Nora Khaldi (Trinity College, Dublin, Ireland) presented intriguing evidence of possible horizontal gene transfer in *Aspergillus oryzae*, the fungus that ferments soy sauce. Its genome contains clusters of genes that are paralogous to dispersed genes already present in the *Aspergillus* lineage. On the basis of gene order in these clusters, the novel paralogs may have been horizontally transferred from a Sordariomycete, the family to which the common coprophilous fungus *Sordaria* belongs. Sordariomycetes, like *Apergillus*, are filamentous ascomycetes.

Gene-expression analysis has implicated paralogs and gene families in human and plant infection. Within the aspergilli, William Nierman (The Institute for Genomic Research, Rockville, USA) and colleagues have identified lineage-specific genes that are unique to each species. Interestingly, these tend to lie in subtelomeric regions and often have paralogs within the genome. The evolutionary forces at play here are unknown, but telomeric sequences may either generate gene duplications or protect them from recombinational loss. Many lineage-specific genes are upregulated during infection, raising the possibility that they contribute to the unique virulence properties of individual *Aspergillus* species. Li-Jun Ma (Broad Institute, Cambridge, USA) and her group are studying repeated sequence content of *Fusarium* species. These sequences are primarily responsible for the widely differing genome sizes (42-60 megabases) of *Fusarium* species. *Fusarium oxysporum*, which has the largest genome, has a high degree of identity among its repeats, suggesting a recent expansion. Remarkably, these repeats are largely restricted to only three chromosomes, and are interspersed with six families of genes encoding secreted proteins that are induced during infection. Thus, these repeated elements may contribute to the broad host range of *F. oxysporum* through effects on evolution or expression of infection-induced genes.

Sexual diversity

Genomic comparisons of closely related species have also shed light on fungal sex, or the lack of it. Two groups have examined how members of the *Aspergillus* and *Candida* genera have lost, and perhaps regained, the ability to produce meiotic progeny. From an analysis of eight *Aspergillus* genomes, Antonis Rokas (Broad Institute, Cambridge, USA) and colleagues found that a homothallic progenitor species (that is, one able to mate with itself) gave rise to heterothallic species (only able to mate with the opposite sex) that eventually gave rise to asexual species. There is plasticity in the evolution of the reproductive lifestyle, as evidenced by *Neosartorya fisheri* (*Aspergillus fisherianus*), which has regained homothallism from a heterothallic ancestor. Geraldine Butler (University College, Dublin, Ireland) and her group have investigated mating loci, pheromone-response pathways, and meiotic genes in the mostly asexual *Candida* species, particularly those that read the codon CTG as serine instead of leucine. Although mating can occur, meiosis has not been observed in several of these fungi, notably the human pathogen *C. albicans*. While pheromone-response pathways are fairly well conserved throughout this group, meiotic genes are not, even in *C. guilliermondii* and *C. lusitaniae*, which are known to have complete sexual cycles. These fungi must employ novel meiotic mechanisms, and identification of the relevant genes will provide new insight into this conserved process.

From a comparison of the mating-type locus (*MAT*) of *S. cerevisiae* and its relatives, Wolfe reported considerable gene instability in a region flanking the locus. Gene truncation and deletion is a common feature of the region between *MAT* and the silent *HML* locus, resulting in greater proximity of *MAT* to *HML* in present-day species compared with the ancestral gene order. *MAT* and *HML* undergo frequent recombination, and perhaps unstable regions in other genomes will turn out to be flanked by similar sequences.

Expression studies and functional genomics

DNA microarrays are available for numerous fungal genomes, and their use has paved the way for targeted functional analysis. Marc-Henri Lebrun (Bayer Crop Science, Lyon, France) and his colleagues have focused on the transition from asymptomatic to symptomatic infection by the rice pathogen, *Magnaporthe grisea*. Lebrun reported that a large number of fungal genes are upregulated during this transition. Many of these genes specify putative secreted proteins of unknown function, thus underscoring that there is much about the mechanism of fungal-host interaction that we have yet to understand.

Expression profiling has moved forward to successful functional analysis for the human pathogen *C. albicans*, for which formation of a biofilm is a key virulence trait. Christophe d'Enfert (Institut Pasteur, Paris, France) and colleagues have used microarrays to identify a set of genes upregulated during biofilm formation under diverse conditions. Among 40 interesting genes from this group, deletion analysis shows that nine are required for normal biofilm formation. Meanwhile, Adnane Sellam (Biotechnology Research Institute, Montreal, Canada) has identified genes uniquely expressed in *C. albicans* cells that break away from biofilms, which are thought to seed systemic human infection. Included among these genes may be some required for the initiation of infection.

Neurospora crassa is the prime model for fungal development and the physiology of filamentous fungi. Inexpensive microarrays and a library of gene deletions are being generated by the *N. crassa* community. Louise Glass (University of California, Berkeley, USA) and her group have explored transcriptional states across the *N. crassa* colony, which is composed of a spectrum of developmental states ranging from linear hyphal growth to hyphal branching to development of asexual spores (conidia). Their findings, including the detection of a large number of genes of unknown function that are upregulated during conidial development, will indeed be crucial for prioritizing and focusing analysis of the gene-deletion collection.

For some fungi, hundreds of public microarray datasets are being analyzed for genome-wide transcriptional modules. This analysis is being carried out both in single species, to identify promotor elements, and across related species, to compare transcriptional responses to a variety of stresses.

Judy Berman (University of Minnesota, Minneapolis, USA) and her collaborators have used 250 microarray datasets from *C. albicans* to create a database of transcriptional modules. They have identified conserved regions (non-TATA and TATA elements) upstream of many of these modules that represent putative promoter elements. The relative positions of these conserved elements are species specific. Looking across species, Dawn Thompson (Broad Institute, Cambridge, USA) and her colleagues are expanding phylogenetic *cis*-element profiling to identify possible regulatory motifs flanking known or inferred gene modules. This project will provide models of global gene regulation that can be tested across divergent species.

Genomes on the move

Updates on several fungal genome sequences were presented at workshops during the conference. Highlights included a report by Luis Corrochano (University of Seville, Seville, Spain) on the draft genome and annotation of *Phycomyces blakesleeanus*, a classic model for fungal sensory physiology. Only the second zygomycete to be sequenced, the genome sequence has already shed light on families of signal transduction proteins involved in sensory perception. Seven fungal genomes near completion were presented at the Dothideomycete workshop. The Dothideomycetes encompass several devastating plant pathogens, affecting a broad range of crops from wheat to bananas. Comparative analysis of these genomes will elucidate the basis for success of these plant pathogens and, hopefully, their Achilles' heels as well.

Fungal research now provides a unique opportunity to connect biology, gene function, and evolution to take systems biology to the next level. Fungal genomes, ranging from model organisms to virulent pathogens, have led to the creation of microarrays, deletion libraries, and proteomic resources, vastly increasing the pace of discovery. The questions being answered will not only affect mycology and medicine, but will also impact on research in other systems as well, as discoveries in fungi are applied to their eukaryotic cousins.

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