FUNGAL PATHOGENESIS

Global control

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URLs

Entrez Genome Project:
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj>

Agrobacterium tumefaciens
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=O>
 view&list_uids=12329

Blastomyces dermatitidis
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=O>
 view&list_uids=12671

Coccidioides posadasii
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=O>
 view&list_uids=10735

Histoplasma capsulatum
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=O>
 view&list_uids=12630

Saccharomyces cerevisiae
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=O>
 view&list_uids=9518

Researchers have identified the regulator of the phase transition from the non-pathogenic hyphal form to the pathogenic yeast form in dimorphic fungal pathogens, according to a paper published recently in *Science*.

Six dimorphic ascomycetes including *Blastomyces dermatitidis* and *Histoplasma capsulatum* are typically found in the environment but can cause disease in humans if spores are inhaled. Temperature is the key environmental cue for fungal dimorphic switching, with the transition occurring with a shift from 25°C to 37°C, but the key outstanding question in the field has been what regulates this phase transition. In this work, Julie Nemecek, Marcel Wüthrich and Bruce Klein set out to identify the master regulator that controls the switch from the hyphal to the yeast form.

Previous work in the Klein laboratory had shown that *Agrobacterium tumefaciens* DNA could be transformed randomly into the *B. dermatitidis* genome and so Nemecek *et al.* devised an insertional mutagenesis assay in which *A. tumefaciens* DNA was transformed into a *B. dermatitidis* reporter strain. Blue/white selection identified seven transformants and the transformant chosen for further analysis had an 86% reduction in transcription of the yeast-phase-specific reporter gene (*BAD1*) compared with the parental strain. Further analysis of the mutant phenotype revealed a pleiotropic set of defects, including the inability to undergo the switch from the hyphal to the yeast form.

The authors went on to map the site of insertion in the *B. dermatitidis* genome and identified the disrupted gene as an open-reading frame

(ORF) encoding a 1274-residue protein. Sequence analysis revealed that this ORF encodes a hybrid histidine kinase with homology to the *Saccharomyces cerevisiae* histidine kinase *SLN1*. Knocking out the ORF by allelic replacement induced the same pleiomorphic defects as observed in the original transformant and so the authors named the gene *DRK1*, for dimorphism-regulating histidine kinase.

In addition to having a homologue in the *S. cerevisiae* genome, *DRK1* is also conserved in the other dimorphic fungal pathogens for which extensive sequence information is available, including *H. capsulatum* and *Coccidioides posadasii*. RNA interference was used

to silence *DRK1* expression in *B. dermatitidis* and *H. capsulatum* and it was found that in *H. capsulatum*, as in *B. dermatitidis*, *DRK1* is involved in dimorphic switching and virulence-gene expression. Finally, *in vivo* analysis showed that the pathogenicity of *DRK1*-silenced strains of both *B. dermatitidis* and *H. capsulatum* was reduced in murine models of infection.

This study represents a milestone in research for those interested in dimorphic fungal pathogens as it not only identifies *DRK1* as a key global regulator that controls the hyphal-to-yeast transition, virulence-gene expression and pathogenicity but also finally confirms that the transition to the yeast form is a requirement for pathogenicity.

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ORIGINAL RESEARCH PAPER Nemecek, J. C., Wüthrich, M. & Klein, B. S. Global control of dimorphism and virulence in fungi. *Science* **312**, 583–588 (2006)