

*cph1* strains make pseudohyphae like the wild type.

How do these varied observations on the control of cell morphology in *Candida* fit together? The most striking observations suggest that the yeast form is the result of negative control of the pseudohyphal growth state. The results of Braun and Johnson, implicating *TUP1*, are particularly provocative because *TUP1* in *Saccharomyces cerevisiae* functions as a global repressor, turning off genes in response to major alterations in the state of the cells. There *Tup1p* protein (together with *Ssn6p*, the product of the *SSN6* gene) controls such processes as cell type ( $\alpha$  or  $\alpha$ ) and glucose repression. *Tup1p* is targeted to a particular site by DNA binding proteins like *Alpha2p* and *Mcm1p* (6, 7); it then acts to block transcription at the adjacent promoter, probably by altering the chromatin structure. *TUP1*-mediated repression is alleviated when the targeting DNA binding protein is no longer present. Interestingly, deletion of *TUP1* in *S. cerevisiae* depresses formation of pseudohyphae.

We are still early in the genetic analysis of the polymorphic character of this fungus, but a working model that incorporates almost all the data can be constructed (see figure). A likely explanation for the Braun and Johnson results is that in the absence of the *TUP1* gene product, the genes for pseudohypha formation are constitutively on. These genes may include a repressor for the yeast genes. The basic feature of the model is that the process is controlled by a series of negative and positive transcription factors, which ultimately affect the TUP-mediated regulation of pseudohyphae and yeast cell formation. In this model, *Efg1p*, the product of the gene studied by Stoldt *et al.* (3), would function as a repressor of the TUP complex (perhaps by repressing the synthesis of the putative DNA targeting protein). Then overexpression of *Efg1p* would block the formation of the TUP complex and allow expression of the pseudohyphal genes. *RBF1* would serve as a repressor of *EFG1*; a deletion of *RBF1* would increase the synthesis of *Efg1p* and lead once more to a decrease in the amount of TUP repression. *Chp1p* would activate the synthesis of *Efg1p*; when *CPH1* is deleted, little *Efg1p* is made, and synthesis of the TUP-complex continues at a high level. Thus, no pseudohyphae can be made. One piece of evidence not accounted for by this model is the pseudohyphal growth of cells in which the amount of *Efg1p* is reduced to a low level. Because *EFG1* is an essential gene, this phenotype may reflect some other function of *Efg1p*. The model in the figure makes several predictions: Overexpression of *Efg1p*, like deletion of *TUP1*, should be epistatic to *CPH1* deletion, but if *Cph1p* is necessary for

the synthesis of *Efg1p*, deletion of *CPH1* should itself be epistatic to deletion of *RBF1*. In other words, the *RBF1-CPH1* double-deletion strain should not form pseudohyphae. Finally, overexpression of *Tup1p* might prevent formation of pseudohyphae under most or all conditions. Given the early state of our analysis of this complex regulatory circuit, many other models can no doubt be devised to suit the data, but the one presented here, although highly speculative, has the advantage of being easily testable.

There are several other implications of this group of papers. Most important, perhaps, is that *C. albicans* should not be thought of as a yeast that can assume various forms. The yeast form exists only if the general repressor *TUP1* is active. A strong case can be made that there is no "default" form for this organism. A second important implication is that hypha formation seems to occur by means of a pathway separate from that for pseudohyphae; none of the deletions or constructs that affect pseudohyphae affect hyphae in similar ways. It also seems likely that alterations in chromatin structure are an important mode of control of morphogenesis in *Candida*; the sort of silencing that has been well studied in *S. cerevisiae* may occur in pseudohyphal genes. Finally, neither deletion of *RBF1* nor overexpression of *Efg1p* completely blocks formation of yeast cells; hence, neither of these alterations causes as profound a change in the cell morphology as the *TUP1* deletion, reinforcing the view that the ultimate control of pseudohypha formation is mediated by a TUP complex.

The role of polymorphism in the pathogenesis of *C. albicans* is far from proven, but the capability seems intuitively important for an organism that is found in a variety of different niches in the body. The elucidation of the regulatory cascade in the papers by Braun and Johnson and others is likely to be of great value in understanding the ways in which this organism causes disease, a topic about which we know little for any pathogenic fungus.

## References

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## Online archaeology

[www.ncl.ac.uk/~nktg/wintro/](http://www.ncl.ac.uk/~nktg/wintro/)

Extensive digging is not necessary to find useful archaeology information at this site, created by K. Greene of the University of Newcastle upon Tyne as an electronic companion to his text "Archaeology—An Introduction." The Web companion is a hyperlinked outline of the book with summaries of chapter contents, supplemented by a thorough set of Web links to other archaeology sites at the end of each section.

## Biocatalysis and biodegradation

[dragon.labmed.umn.edu/~lynda/index.html](http://dragon.labmed.umn.edu/~lynda/index.html)

Understanding biocatalytic reaction pathways is important for both pollution control and applications in biotechnology. The University of Minnesota Biocatalysis/Biodegradation Database aids learning about these reactions and provides extensive links to Web resources on microbial enzyme-catalyzed chemistry. Each chemical pathway is described in text and is accompanied by a graphical representation of the reaction. There is also a graduate level course on biocatalysis offered over the Internet by the site's creators L. Ellis and L. Wackett.

## Neuro net

[www.neuroguide.com](http://www.neuroguide.com)

"Neurosciences on the Internet" is part Web guide and part electronic journal created by N. Busis of Shadyside Hospital, Pittsburgh. The site has a large set of pointers to Web, gopher, mail list, and ftp resources of interest to neuroscientists, including links to image repositories and software collections. In addition, the Web site publishes original contributions vetted by peer reviewers on topics ranging from amyotrophic lateral sclerosis to viral infections in the central nervous system.

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