and is currently unexplained. It certainly exposes the inadequacy of our understanding of the quasiparticles and perhaps the ground state itself, just at a time when there is a sense of confidence that the *d*-wave description of the cuprate superconductors may be established. Further experimental and theoretical work will be needed before we can tell whether we can get away with a minor modification of our current understanding, or whether a more profound revision is called for.

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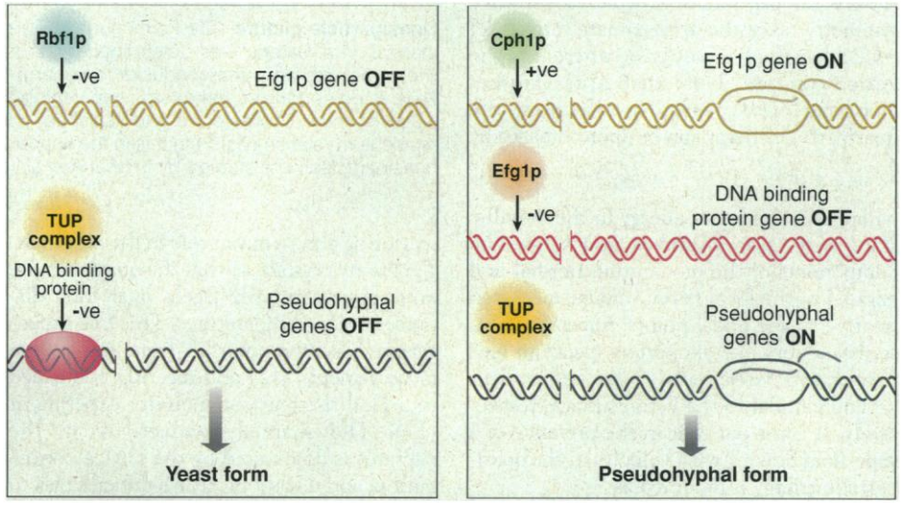
TRANSCRIPTION

Which Came First, the Hypha or the Yeast?

P. T. Magee

Fungal diseases have become a major medical problem in the last few years and are likely to increase in severity. Most fungal pathogens are opportunists, so their emerging importance is due paradoxically to the success of modern medical practices: These diseases thrive in debilitated patients, who now survive much longer than before and are often treated with procedures (such as bone marrow transplants) that diminish their immune responses. The major fungal pathogen in such patients is *Candida albicans*, which can grow in a variety of forms, ranging from budding yeast to threadlike hyphae. Pseudohyphae, which vary in shape from attached strings of yeastlike cells to long filaments with constrictions at the septae, constitute a third form. Thus, C. *albicans* is not, as usually described, dimorphic, but is more properly considered polymorphic; the relations among the various morphological forms are not well understood. The report by Braun and Johnson (*1*) on page 105 of this issue provides exciting information about polymorphism in this organism and, together with two other recent reports (*2*, *3*), will make investigators think in new ways about how C. *albicans* regulates its cell shape.

Braun and Johnson demonstrate that C. *albicans* requires the general transcriptional repressor *TUP1* to maintain the yeast form. When both copies of the *Candida TUP1* gene are deleted (phenotype designated Tup$^-$), the organism grows exclusively in the pseudohyphal form. The general view has been (as the authors state) that the "default" form is the yeast, and some induction mechanism is necessary to cause the morphological change. The filaments that occur under most laboratory conditions in the Tup$^-$ strain are pseudohyphae, but true cylindrical hyphae are found under certain conditions. In an analogous finding, Ishii *et al.* (*2*) report that disruption in C. *albicans* of both copies of the *RBF1* (RPG-box binding factor 1) gene, a putative transcription factor, leads to pseudohyphal growth on a variety of media. Furthermore, Stoldt and co-workers (*3*) show that drastically decreasing the cellular concentration of a Myc-like transcription factor, Efg1p (enhanced filamentous growth), leads to a cellular morphology somewhat like pseudohyphae, whereas overexpression of the *EFG1* gene causes a very strong pseudohyphal phenotype. All these results suggest that pseudohypha formation is under negative control. Although it still may be true that some transcriptional activator is required for the yeast-to-pseudohypha transition, Braun and Johnson show that a previously identified transcriptional activator, *CPH1* (also known as *ACPR*) (*4*), is not. In wild-type C. *albicans*, deletion of both copies of *CPH1* prevents pseudohypha formation (*5*), but strains in which both copies of *TUP1* and both copies of *CPH1* are deleted show the Tup$^-$ phenotype—constitutive filamentous growth. *TUP1*/*tup1* heterozygotes suppress the *cph1*/*cph1* phenotype; that is, *TUP1*/*tup1* *cph1*/



A model for the regulation of pseudohyphal growth in *C. albicans*. The genes required for pseudohyphal growth are under the negative control of a complex consisting of Tup1p and probably other proteins. When this complex is targeted to the pseudohyphal genes by a DNA binding protein, the genes are off (**left**). When the DNA binding protein is absent, the genes are transcribed and the cell grows in the pseudohyphal form (**right**). The DNA binding protein is negatively regulated by Efg1p; when *EFG1* is overexpressed, synthesis of the DNA binding protein is prevented and the cells are in the pseudohyphal state, as shown on the right. *EFG1* is negatively regulated by Rbf1p and positively regulated by Cph1p when the latter is activated by the MAP kinase cascade. When *RBF1* is deleted, Efg1p is overexpressed and the pseudohyphal genes are on. When *CPH1* is deleted, Efg1p is not made and the cells cannot turn on the pseudohyphal genes.

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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 (**a** or α) 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.

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WEBWATCH

Online archaeology

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

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 represention 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

"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.

Edited by David Voss

Readers are invited to suggest excellent scientific Web sites by e-mail to editors@aaas.org.