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Genetics

Reversal of cell determination in yeast meiosis: Postcommitment arrest allows return to mitotic growth

(commitment/sporulation/*Saccharomyces cerevisiae*/transdifferentiation)

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ABSTRACT **When yeast from the early stages of meiosis are transferred from sporulation to growth medium, they can reenter the mitotic cell cycle directly. In contrast, cells from later stages of meiosis (after the initiation of the first nuclear division) will complete meiosis and sporulation despite the shift to growth medium, a phenomenon known as "commitment to meiosis." This study reports the surprising finding that when the normal progression of meiosis is arrested, cells from later stages of meiosis can return to growth. Cells were arrested after the first or second meiotic division by three independent means: the *spo14* mutation, the *spo3-1* mutation, and a high-temperature arrest of wild-type cells. In every case, the arrested cells were able to form buds after transfer to growth medium. These cells, however, experienced a delay upon return to growth relative to uncommitted cells. We propose that the commitment phenomenon results from a transient delay of mitotic growth, which occurs specifically during meiosis, and that commitment does not involve an irreversible inhibition of mitosis as previously thought.**

In many developing systems while cell fate is initially specified by extracellular signals, cells remain determined once these signals are removed. In the last several years, dramatic progress has been made in identifying the ligands and receptors that initiate cell determination. These functions, notably tyrosine kinase receptors, are conserved in a wide range of organisms (1). In contrast, comparatively little is known of the transition, generally termed commitment, that renders cell fate independent of environment. Evidence for commitment has been established in a number of experimental systems by removing partially differentiated cells from their natural environment. These cells remain stably determined and can complete normal differentiation under appropriate conditions, indicating that the maintenance of the determined state is independent of extracellular signals (2, 3).

Meiosis and sporulation in the yeast *Saccharomyces cerevisiae* provide an excellent model system for examining cell determination and commitment, since both the environment of the cell and individual genes can be easily manipulated. Diploid yeast can follow two alternative cell division pathways: mitotic division and growth or meiosis and sporulation. The meiotic fate is triggered by deprivation of glucose and nitrogen. As is true in many types of cell differentiation, cells in meiosis remain uncommitted through the early stages of the process—i.e., they will abort meiosis and return to mitotic growth if the cells are transferred from sporulation to growth medium (4). Significantly, genetic and cytological analyses have revealed that meiotic DNA replication, synaptonemal complex formation, chromosome pairing, and DNA recombination all occur during this uncommitted period (5–7). In contrast, cells become fully committed to meiotic development at the initiation of chromosome segregation in meiosis I—i.e., after this point they will complete the two meiotic divisions and form spores despite the addition of glucose and nitrogen. This study presents the unexpected result that when meiotic cells are arrested after either the first or second division, cells are able to return to mitotic growth. Further experiments suggest that commitment results from a transient delay in mitotic growth rather than an irreversible inhibition of the cell cycle during sporulation.

MATERIALS AND METHODS

Strains. The following diploid strains were used in this study. H65 contains *MATa/MATα ADE2/ade2-1 ade5/ADE5 can1/can1 CYH2/cyh2 HIS1/his1 his7/HIS7 HOM3/hom3-10 leu2-3/leu2-1 lys1/LYS1 LYS2/lys2 met14/MET14 pet8/PET8 TRP1/trp1 ura3/ura3*. H91 is isogenic to H65 except for the presence of a homozygous disruption/duplication allele of *SPO14* designated *spo14:URA3:spo14* (8). REE1525 contains *MATa/MATα arg4-1/arg4-1 cyh1-1/cyh1-1 HO/HO met4/met4*. SH495 is congenic to REE1525 and is *spo3-1/spo3-1*.

Media. Growth (YPDA) and acetate (YPA) media have been described (8). The sporulation media (SPII-30 and SPII-31) contain 20 g of potassium acetate per liter supplemented with 75 μg (each) of either adenine sulfate, L-leucine, and uracil per ml (for strains H65 and H91) or L-arginine and L-methionine (for strains REE1525 and SH493).

Assaying Landmark Events in Meiosis. Fifty-milliliter cultures were grown for ≈20 hr at 30°C in YPA to 5.0×10^7. Cells were washed three times, resuspended in 25 ml of sporulation medium (pH 6.5), and aerated by shaking at constant temperature in a New Brunswick Scientific gyratory water bath shaker at 250 rpm. At intervals, 200-μl samples were fixed by addition of 400 μl of 95% ethanol. An aliquot (6 μl) of this cell suspension was spotted on a microscope slide and allowed to dry. Nuclei were stained by placing 6 μl of a solution of 1 μg of 4′,6-diamidino-2-phenylindole dihydrochloride per ml (DAPI, Boehringer Mannheim), 0.1 mg of 1,4-phenylene diamine per ml (Sigma), 50 mM sodium phosphate buffer, and 50% glycerol on the dried cells. Cells were visualized by Nomarski/fluorescence microscopy on a Jenalumar microscope. Two hundred to 300 cells were counted for each sample. DNA content was determined by DNA staining with propidium iodide (Sigma) followed by flow cytometry (9) using a Becton Dickinson FACScan 4 flow cytometer and LYSYS II software. Meiotic intragenic recombination was assayed at the *leu2* locus by plating cells on synthetic compete medium lacking leucine.

Return-to-Growth Experiments. At intervals during sporulation, 0.5-ml samples were transferred to 9.5 ml of pre-

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Abbreviation: DAPI, 4′,6-diamidino-2-phenylindole dihydrochloride.

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warmed YPDA and aerated by shaking. At various times, aliquots (1 ml) were removed from the YPDA cultures, washed once with distilled H_2O, resuspended in 100 μl of distilled H_2O, and fixed by the addition of 200 μl of 95% ethanol. Nuclei were stained as described above. Immunofluorescent staining of spindles was performed as described (10), except that Zymolyase 20T (ICN) was substituted for 100T.

RESULTS

Wild-Type Meiosis I Binucleate Cells Complete Meiosis II and Spore Formation After Transfer to Growth Medium. In wild-type cells, chromosome segregation at meiosis I results in "binucleate" cells, as visualized by DAPI nuclear staining and fluorescence microscopy. These convert to "tetranucleate" cells at the completion of the meiosis II division and then form spores to yield tetrad asci. Electron microscopy reveals that the nuclear envelope in yeast remains intact around the separated chromatin masses throughout meiosis.

In a control experiment, a wild-type culture was sporulated until 10–15% of the cells had completed meiosis I and become binucleate. The culture was then shifted to growth medium and continued progression of these binucleate cells through meiosis measured by the appearance of tetranucleate cells and tetrad asci (Fig. 1*A*, circles) and the disappearance of binucleate cells (Fig. 1*B*, left panel). The ability of cells that have completed meiosis I to return to growth was assayed by the appearance of buds associated with binucleate cells (Fig. 1*B*, left panel). Both criteria indicate that wild-type binucleate cells do not form buds or return to growth; instead, they proceed through meiosis and sporulation, in agreement with prior studies (see the Introduction). Equivalent observations were made for wild-type tetranucleate cells in this and another strain background (cf. Fig. 1 *C* and *D*, left panel).

Temperature-Arrested Wild-Type Binucleate Cells Can Return to Growth Directly Without Completing Meiosis. Our interest in commitment arose during the characterization of *spo14*, a new mutant defective in sporulation (8). In *spo14* mutants, the second meiotic division and spore formation are defective (Fig. 1*A*, triangles), while earlier meiotic events are largely unaffected (Table 1). This results in the accumulation of binucleate cells during meiosis. Surprisingly, these binucleate cells form buds when transferred to growth medium (Fig. 1*B*, compare left to middle panel); furthermore, these cells continue to divide and yield viable products (8). Since

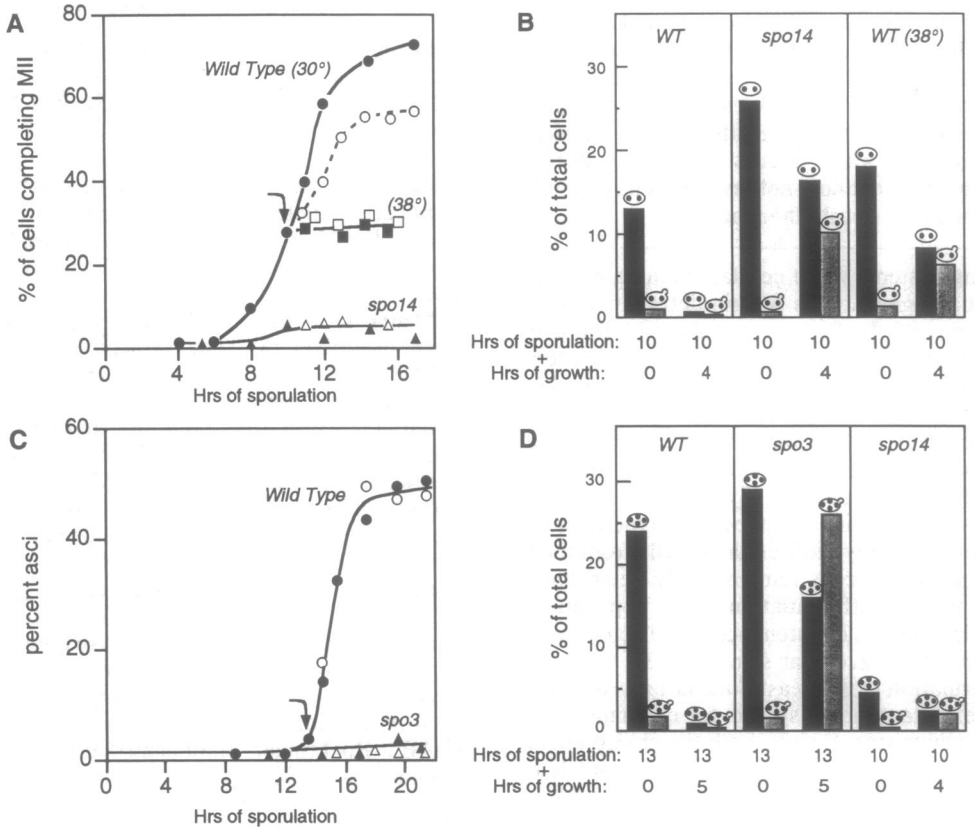

FIG. 1. Completion of meiosis vs. return to mitotic growth in wild-type and arrested meiotic cells. (*A*) Meiosis II in wild-type and *spo14* cells. The % cells completing meiosis II (tetranucleate cells plus tetrad asci/total cells) was monitored in a wild-type strain (circles) and in an isogenic *spo14* disruption (triangles) at 30°C, and in the wild-type after shifting to 38°C at 9 hr of sporulation (squares). At 10 hr, cells from sporulation culture were transferred to growth medium, and their progress through meiosis II (open symbols, transfer indicated by arrow) was compared to those remaining in sporulation medium (closed symbols). In the wild type, 64% of the total cells form tetrad asci after 17 hr of sporulation, compared to 46% tetrad asci after 10 hr of sporulation followed by 7 hr in growth medium; in the *spo14* mutant, <0.1% of the cells form asci under either condition. (*B*) Return to growth of binucleate cells arrested in meiosis. The fraction of binucleate cells without buds (solid bars) or with buds (stippled bars) was measured after 10 hr of sporulation or 10 hr of sporulation followed by 4 hr in growth medium: wild-type (left panel), *spo14* disruption at 30°C (middle panel), and wild-type transferred to 38°C at 9 hr (right panel). The % binucleate cells in the wild-type decreases after transfer to growth medium as these cells complete meiosis and form asci. (*C*) Spore formation in wild-type and *spo3-1* cells. Asci were monitored in a wild-type (circles) and a *spo3-1* strain (triangles) in sporulation medium (closed symbols), or following transfer to growth medium after 13 hr of sporulation (open symbols, transfer indicated by arrow). (*D*) Return to growth of tetranucleate cells arrested in meiosis. The fraction of tetranucleate cells without buds (solid bars) or with buds (stippled bars) was measured after 10–13 hr in sporulation medium or after 10–13 hr in sporulation medium followed by 4–5 hr in growth medium: wild-type (left panel), *spo3-1* (middle panel), and *spo14* disruption (right panel).

Table 1. Sporulation defects employed in this study

Meiotic defect	% of wild type				
	DS	Rec	MI	MII	Asci
spo14::URA3	110	84	57	7	0.1
WT, shift to 38°C	NA	NA	NA	3	3
spo3-1	100	100	64	48	1

Values are expressed as the maximum percentage of cells completing a given meiotic event standardized to the maximum percentage of cells that complete this event in a control sporulation culture. WT, wild type; DS, DNA replication; Rec, recombination; MI, chromosome segregation in meiosis I; MII, chromosome segregation in meiosis II; Asci, spore formation. For the *spo14::URA3* mutant (H91), the control is an isogenic wild-type strain, H65, in which 80% of the cells complete sporulation. In the shift to 38°C experiment, the control is H65 without a temperature shift. DS, Rec, and MI are largely complete at the time of the temperature shift and therefore are not affected (NA); the data show the progress of cells through meiosis *after* the temperature shift. For the *spo3* strain (SH495), the data for DS and Rec are from ref. 11 and ref. 7, respectively. The control culture for MI, MII, and Asci is the congenic wild-type strain REE1525 in which 65% of the cells complete sporulation.

this mutant returns to growth from the point of arrest, we considered the possibility that the ability to reenter mitosis from the binucleate stage results from blocking the further progression of meiosis. If this were the case, then an environmental condition that also arrests wild-type cells at the binucleate stage should similarly allow return to growth. Since high temperature (above 35°C) typically inhibits sporulation of wild-type strains (12), the effect of high temperature on late meiotic events was examined. Meiosis was induced in wild-type cells using a standard sporulation regimen (starvation for glucose and nitrogen at 30°C). Cells were allowed to reach the binucleate stage at 30°C and then shifted to 38°C. Fig. 1*A* shows that at the higher temperature further progression of meiosis is inhibited (see also Table 1). Significantly, when the arrested binucleate cells are transferred to growth medium, they bud and return to mitotic growth (Fig. 1*B*, right panel), similar to the previous results with *spo14* binucleate cells. Two examples of temperature-arrested binucleate cells in the course of budding are shown in Fig. 2*A*.

Cells Arrested After Meiosis II by the *spo3-1* Mutation Can Return to Growth Without Completing Spore Formation. To determine if cells could return to growth from an even later stage in sporulation, a second mutant, *spo3-1*, was utilized. This mutant allows both meiotic divisions, forming tetranucleate cells, but does not enclose the four nuclei into spores (Table 1 and Fig. 1*C*) (13). Like the arrested binucleate cells discussed above (and unlike wild-type cells), when *spo3-1*-arrested tetranucleate cells are shifted to growth medium they form buds and reenter the mitotic cell cycle (Fig. 1*D*, compare left and middle panels; Fig. 2). A *spo3-1* tetranucleate cell that contains an anucleate bud and another one that contains a nucleus in the bud are shown in Fig. 2*B*. That

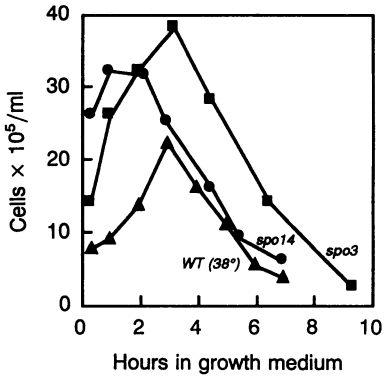

FIG. 3. The number of multinucleate cells decreases after transfer to growth medium. The ordinate indicates the total number of multinucleate cells (unbudded and budded) per ml from a given stage in meiosis. The abscissa indicates the time elapsed after shifting cells from sporulation medium to growth medium. For each sample, the percentage of multinucleate cells was multiplied by the total cell concentration, yielding total multinucleate cells per ml. This allows representation of multinucleate cell number independent of the increasing cell density of the culture. After 10 hr of sporulation (a sufficient time for binucleate cells to accumulate), aliquots were transferred to growth medium, and the number of binucleate cells was monitored either in a *spo14/spo14* strain (H91) at 30°C (circles) or in a wild-type strain (H65) at 38°C (triangles). Similarly, after sufficient time in sporulation medium to accumulate tetranucleate cells (13.5 hr), a *spo3-1/spo3-1* strain (SH495) was transferred to growth medium and the level of tetranucleate cells was monitored (squares).

arrested tetranucleate cells are capable of returning to mitotic growth is also seen in the small fraction of *spo14* mutants that escape the meiosis II block (≈5% of *spo14* cells reach the tetranucleate stage but these never form spores; see Fig. 1*A* and Table 1). Like the *spo3*-arrested cells, these tetranucleate cells also bud and return to mitosis when transferred to the appropriate medium (Fig. 1*D*, right panel; see Fig. 4).

Do different nuclei in a multinucleate cell return to growth independently? Of 200 *spo3*-arrested cells containing anucleate buds that were examined, none contained more than a single bud. However, in rare cases where the mother and daughter cells remain associated, a second nuclei in the mother cell appears to form a bud at approximately the same time as the daughter cell forms its own bud (Fig. 2*C*). This suggests that a single multinucleate cell is capable of segregating the different nuclei into buds in subsequent rounds of the mitotic cell cycle but not in the same round.

In summary, three independent conditions that block the progression of meiosis at late stages (the *spo14* mutation, the high-temperature phenocopy condition, and the *spo3-1* mutation) enable the arrested cells to return to mitosis; in contrast, wild-type cells from these same stages will complete meiosis and sporulation in growth medium. The simplest

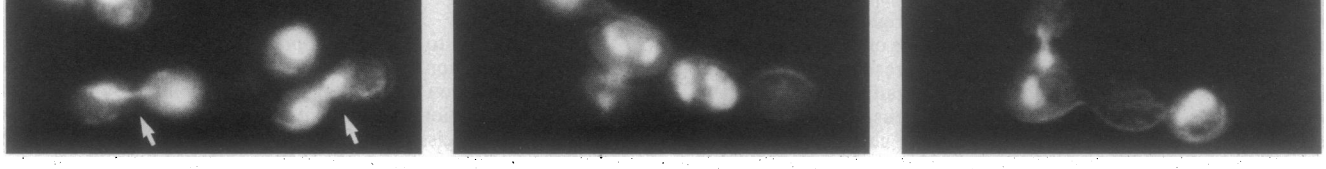

FIG. 2. Return to growth of cells arrested in "postcommitment" stages of meiosis. Nuclei were stained with DAPI and photographed through Nomarski/fluorescence optics. (*A*) Arrows indicate two examples of wild-type binucleate cells in which one of the two nuclei is migrating into a newly formed bud. Cells were sporulated for 10 hr and then transferred to growth medium at 38°C for 5 hr. (*B*) Two examples of *spo3-1* tetranucleate cells that are in the process of budding. Cells were sporulated for 13 hr and then exposed to growth medium for 4 hr. (*C*) A *spo3-1* tetranucleate cell that has undergone several divisions. This cell was sporulated for 13 hr and then exposed to growth medium for 7 hr. These cells are rare; more commonly, *spo3-1* tetranucleate cells undergo complete cell separation after each division. (×1600.)

explanation for these results is that interruption of meiosis is sufficient to allow the arrested cells to return to growth.

Mitotic Growth from Multinucleate Cells. How do binucleate and tetranucleate cells return to growth? Although it is not always feasible to follow the nuclei of an individual cell as it buds and returns to growth (fluorescence visualization generally prevents further growth of the cell), a combination of microscopy and genetic analysis allows reconstruction of the principle events of this process. While the general mechanism of return to growth is not yet known, the following observations suggest that one nucleus of a multinucleate cell migrates into the new bud and then reenters the mitotic cycle at the G_1 stage.

Immediately after transfer to growth medium, unbudded binucleate cells decrease in the population as *budded* binucleate cells appear (Fig. 1*B*). Later, the absolute number of binucleates declines rapidly (Fig. 3, triangles and circles) without any increase in the total number of tri- and tetranucleate cells (Fig. 1*A*, open squares and triangles; Fig. 1*D*). These data favor a mechanism in which the binucleate cells, instead of undergoing a new round of nuclear division of one or both nuclei upon return to growth, undergo a transfer of one of the two meiosis I nuclei to the bud to give rise to mononucleate mother and daughter cells. Similar results were also obtained for *spo3*-arrested tetranucleate cells; they first form buds (Fig. 1*D*) and then their absolute number decreases rapidly in the population (Fig. 3), and cells with more than four nuclei are not seen.

Other evidence comes from genetic characterization of colonies formed after *spo14*-arrested meiotic cells are returned to growth (8). For each chromosome tested, these colonies were shown to be homozygous diploids, containing two copies of one parental chromosome and no copies of its homolog. Their phenotypes are consistent with transfer and propagation of a single diploid nucleus of a meiosis I binucleate cell into the daughter. Their origin is incompatible with one diploid nucleus undergoing mitosis into the bud in the absence of an S phase (as that would generate haploid daughters) and one nucleus undergoing an S phase then mitosis into the bud (as the absolute number of binucleates should remain constant).

A final line of evidence is based on the finding that although the majority of *spo14* cells arrest as binucleates, a minority of the cells (5%) reach the tetranucleate stage. Transfer of these cells to growth medium is particularly informative because of the two meiosis II spindles present in tetranucleate cells (tubulin staining of these cells is also much clearer than in *spo3* cells). Eighty tetranucleate cells in which at least one nucleus is present in the bud were examined; these often reveal a spindle that extends from a nucleus in the mother to one in the bud (Fig. 4 *A–D*), suggesting that the preexisting meiotic spindle is reoriented during the initial cell division to promote migration of one of the nuclei into the new bud. Consistent with this view is the observation that the nucleus still in the mother cell is usually near the bud neck (Fig. 4 *A–D*) and that in some cells it appears that one spindle connecting two nuclei has entirely migrated into the daughter cell (Fig. 4 *E* and *F*).

Arrested Binucleate Cells Return to Mitotic Growth More Slowly than Mononucleate Cells. What causes a cell to become committed to meiosis (14–16)? One explanation is that in the course of meiosis, cells lose the machinery necessary to return to the mitotic cycle, for example, by losing receptors for glucose or nitrogen. However, the demonstration that arrested binucleate and tetranucleate cells can return to growth rules out models that involve irreversible changes in the cell. Rather, it suggests that commitment is caused by transiently repressing mitosis and that this regulatory state can be reversed with time. By this view, when cells are blocked in meiosis, they eventually become derepressed for mitotic functions and can return to mitotic growth. Support

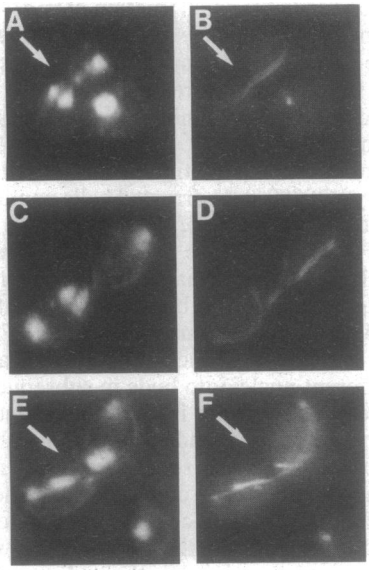

FIG. 4. Visualization of spindles in multinucleate cells after return to growth. A *spo14* strain (H91) was exposed to sporulation medium for 16 hr at 30°C and then transferred to growth medium for an additional 6 hr. Each pair of photographs shows the same cell stained with DAPI (left) or by anti-tubulin (right). (*A* and *B*) Cell indicated by arrow. A long spindle connects one of two nuclei present in the (putative) mother cell with a nucleus present in the daughter cell. (*C* and *D*) Two of three nuclei in the (putative) mother cell are connected by a spindle, while the third nucleus is connected by a second spindle to a nucleus in the daughter cell. (*E* and *F*) Cell indicated by arrow. One pair of nuclei are present in each cell, each pair connected by a spindle. Both spindles are aligned and perhaps connected. Ninety-four percent (283/300) of the total cells in the culture stain with both DAPI and anti-tubulin. Thirty-seven percent of multinucleate cells (30/80) contain a long spindle like those shown here; the remaining cells contain spindle pole bodies (38/80) or short spindles (9/80) associated with each nucleus. (×1750.)

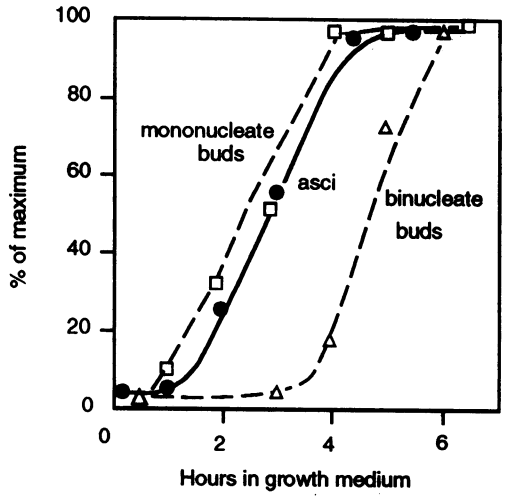

FIG. 5. Return to growth of *spo14* binucleate cells is delayed relative to completion of sporulation in wild-type cells. The ordinate indicates the fraction of cells that have either initiated budding or completed sporulation as a percent of the maximum levels of these processes; the abscissa indicates the time after transfer of a 10-hr sporulation culture to growth medium. Samples were removed periodically, fixed, and examined by Nomarski/fluorescence microscopy for bud emergence in binucleate (triangles) and mononucleate (squares) cells of the mutant and spore formation in the wild-type strain (circles). At maximum, 56% of the total binucleate cells and 52% of the total mononucleate cells contained buds; at maximum, 46% of the total cells completed sporulation.

for this idea comes from comparing the rate of return to growth in a *spo14* culture to the rate of completion of meiosis in a wild-type culture (Fig. 5). Although more than half of *spo14*-arrested binucleate cells initiate budding upon transfer to growth medium, bud emergence occurs only after a lag of several hours (Fig. 5, triangles). In contrast, mononucleate (i.e., *uncommitted*) cells from the same *spo14* culture return to mitotic growth much more rapidly (Fig. 5, squares), consistent with the idea that mitotic functions are transiently repressed in committed cells. Although mitotic repression in committed cells is not permanent, it is sufficiently long to allow the completion of sporulation in growth medium when meiosis is not arrested (Fig. 5, circles)—i.e., it is sufficient to cause commitment. This time delay in returning to growth may reflect the time required to reprogram the regulatory state of the cell.

DISCUSSION

After the initiation of chromosome segregation in meiosis I, yeast cells are able to complete meiosis and sporulation even if transferred to growth medium, a phenomenon termed "commitment to meiosis." The primary result described in this paper is that commitment is a reversible process: if meiosis is arrested, cells from the postcommitment stages of the meiotic pathway can reenter the mitotic cell cycle; they are not "stuck in the meiotic program." What does it mean for a cell to be "committed to meiosis," given that this commitment is reversed when cells are arrested? One explanation is that commitment occurs when the time period required for reinitiating mitotic growth exceeds the time required for completing meiosis. This idea, called the "kinetic choice" model for commitment, was suggested to explain how *spo14*-arrested binucleate cells are able to return to growth (8). By this argument, commitment is reversible when meiosis is blocked because now the cells have sufficient time to return to the mitotic cycle. The results presented in this paper strongly support this idea since arresting meiosis by any of three different means can reverse commitment, indicating that blocking differentiation allows this reversal regardless of the cause of the arrest.

The second major finding described above is that the resumption of mitotic growth from arrested postcommitment cells is delayed relative to uncommitted cells. While the original version of the kinetic choice model proposed that the commitment process need not "specifically inhibit mitotic functions," the results shown in Fig. 5 suggest that mitotic functions are, in fact, inhibited. We found that cells arrested after the time of commitment return to mitotic growth after a long delay (4 hr) relative to uncommitted cells from the same culture (1 hr). This last result indicates that the commitment process involves functions that (transiently) inhibit the response to growth signals. In summary, commitment is understood as a kinetic difference between the completion of meiosis (fast) and the response to nutrients (slow). This mechanism for delaying the response to nutrients in committed cells may represent a novel means of controlling differentiation.

Meiotic cells arrested at the binucleate and tetranucleate stage and allowed to return to mitosis may prove useful for examining the mechanics of mitotic cell division. Our results are most consistent with multinucleate cells returning to growth via a pathway in which a nucleus migrates into a new bud and resumes the mitotic cell cycle at the G_1 stage. Nuclear migration to the bud neck occurs prior to mitosis in yeast and also occurs before nuclear fusion during mating. Although migration of a nucleus into a new cell body without nuclear division is not normally seen in wild-type yeast, it is common in some other fungi and in algae (17). Furthermore, examination of several *S. cerevisiae* mutants (e.g., *num1* and *dhc1*) that transiently generate binucleate cells during mitosis has led to the suggestion that the daughter nucleus migrates into the bud *after* mitosis in these mutants (18, 19). Time-lapse photography of a binucleate cell that is undergoing such a nuclear migration support this view (Ayumu Yamamoto and Doug Koshland, personal communication). In line with the behavior of these mitotic mutants, one way to explain our results is to say that migration of preexisting meiotic spindles in multinucleate cells results in the segregation of one nucleus into the daughter cell. In many cases it appears that two sister nuclei still connected by a meiosis II spindle move together into the new bud, suggesting an interaction of either the spindle or the nuclei with an intracellular matrix.

In a variety of developmental systems, determined or even terminally differentiated cells can revert to other developmental fates under special circumstances, a phenomenon known as transdifferentiation. Two examples of this reversal in cell fate are the regeneration of cells of the retina from surrounding cells of different type and the conversion of determined imaginal disk cells in *Drosophila* to alternate fates after prolonged growth in culture (20, 21). The findings reported here suggest that in the case of yeast meiosis, simply blocking the preferred developmental pathway can be sufficient to allow previously committed cells to adopt a mitotic rather than a meiotic fate. Acquisition of an alternate fate as a result of a defect in normal differentiation, and particularly regaining the capacity for mitotic growth and division as a result of blocking the progression of development, could be involved in other examples of transdifferentiation, in oncogenesis, and in the normal adaptation of developing cells to environmental variations.

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1. Greenwald, I. & Rubin, G. M. (1992) *Cell* **68**, 271–281.
2. Gehring, W. (1978) in *Imaginal Discs: Determination*, eds. Ashburner, M. & Wright, T. R. F. (Academic, New York), pp. 511–555.
3. Gurdon, J. B. (1992) *Cell* **68**, 185–199.
4. Ganesan, A. T., Holter, H. & Roberts, C. (1958) *C. R. Lab. Carlsberg* **13**, 1–6.
5. Sherman, F. & Roman, H. (1963) *Genetics* **48**, 255–261.
6. Simchen, G., Pinon, R. & Salts, Y. (1972) *Exp. Cell Res.* **75**, 207–218.
7. Esposito, R. E. & Esposito, M. S. (1974) *Proc. Natl. Acad. Sci. USA* **71**, 3172–3176.
8. Honigberg, S. M., Conicella, C. & Esposito, R. E. (1992) *Genetics* 130, 703–716.
9. Hutter, K. J. & Eipel, H. E. (1979) *J. Gen. Microbiol.* **113**, 369–375.
10. Rose, M. D., Winston, F. & Hieter, P. (1990) *Methods in Yeast Genetics: A Laboratory Course Manual* (Cold Spring Harbor Lab. Press, Plainview, NY).
11. Esposito, M. S. & Esposito, R. E. (1974) *Genetics* **78**, 215–225.
12. Byers, B. & Goetsch, L. (1982) *Mol. Gen. Genet.* **187**, 47–53.
13. Moens, P. B., Esposito, R. E. & Esposito, M. S. (1974) *Exp. Cell Res.* **83**, 166–174.
14. Esposito, R. E. & Klapholz, S. (1981) in *Meiosis and Ascospore Development*, eds. Strathern, J. N., Jones, E. W. & Broach, J. R. (Cold Spring Harbor Lab. Press, Plainview, NY), pp. 211–287.
15. Murray, A. W. & Szostak, J. W. (1985) *Annu. Rev. Cell Biol.* **1**, 289–315.
16. Mitchell, A. P. (1988) in *Meiotic Inhibition: Molecular Control of Meiosis*, eds. Haseltine, F. P. & First, N. L. (Liss, New York), pp. 47–66.
17. Url, T., Hoeftberger, M. & Meindl, U. (1992) *J. Phycol.* **28**, 537–544.
18. Okada, T. S. (1991) *Transdifferentiation: Flexibility in Cell Differentiation* (Oxford Univ. Press, New York).
19. Hadorn, E. (1965) *Brookhaven Symp. Biol.* **18**, 148–161.
20. Kormanec, J., Schaaff-Gerstensclager, I., Zimmerman, F. K., Perecko, D. & Kuntzel, H. (1991) *Mol. Gen. Genet.* **230**, 277–287.
21. Li, Y., Yeh, E., Hays, T. & Bloom, K. (1993) *Proc. Natl. Acad. Sci. USA* **90**, 10096–10100.