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MICROBIAL GENETICS:

Love the one you're with

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Candida albicans is notorious as an opportunistic infection that causes thrush and serious systemic disease. For geneticists, however, it offers continuing revelations into the wondrously varied sex lives of fungi.

Sex facilitates evolution by recombining parental genomes and purging deleterious mutations. There are myriad forms, but they have three steps in common: meiosis, which halves the number of chromosomes per cell; gamete production; and cell–cell fusion. Sex in animals involves two individuals of opposite sex, male and female, which produce distinct gametes (sperm and oocytes). In fungi, sex typically involves morphologically similar cells of opposite mating-type (**a** and **α**) that reciprocally produce sex-stimulating pheromones. In other cases, fungi are self-fertile and lone individuals sexually reproduce. One well-known example is the model yeast species, *Saccharomyces cerevisiae*, in which a single cell divides, switches mating-type, and mating yields **a/a** diploid cells, with a double complement of chromosomes, that no longer mate but undergo meiosis. On page 000 of this issue, Alby *et al.*¹ report a conceptually similar, yet mechanistically distinct self-mating phenomenon in another yeast, the pathogenic *Candida albicans*.

Candida albicans resides in the human microbiota, for example in the gastrointestinal tract, and commonly causes infections. For more than a century, it was thought to be strictly asexual. Then the mating-type gene locus was discovered, and most isolates were found to be **a/a** diploids that, like *S. cerevisiae*, are sterile². Mutants with only one mating-type (**a/a**, **α/α**) were found to mate in the laboratory or during infection². But the low frequency of mating raised the question of whether sex occurs in nature. This concern was resolved by various discoveries^{2–4}, including the observation that mating is enhanced one million-fold when cells switch from white to an opaque type specialized for mating.

In opposite-sex mating in *C. albicans* (Fig. 1a), cell–cell fusion produces tetraploid cells that have four copies of each chromosome (**a/a/α/α**). These tetraploids undergo a ‘parasexual’ phase⁵, which restores the diploid state and allows limited genetic recombination but does not involve overt meiosis and does not produce spores. (The parasexual recombination that does occur requires Spo11 (ref. 6), an enzyme that acts as a recombinase during meiosis in other organisms. Thus, *C. albicans* sex could involve cryptic meiosis or novel parasexual roles for Spo11.)

Alby *et al.*¹ report the discovery of a facet of *C. albicans* reproduction in which cells mate with each other via same-sex mating (Fig. 1b), rather than with the opposite mating type. This observation arose from analysing *C. albicans* mutants lacking an enzyme, barrier protease, which inactivates **α**-pheromone. Barrier was discovered in *S. cerevisiae* as a factor interfering with mate signalling when **a**-cells producing barrier are interposed between **a**- and **α**-cells⁷. Among other things, we now know that barrier is encoded by the *BAR1* gene in a mating-type-specific fashion, and that it acts on **α**-pheromone, enabling **a**-cells to choose mates producing the most pheromone.

Curiously, *C. albicans* **a**-cells express genes encoding both **a**- and α -pheromone. Alby *et al.*¹ observed that **a**-cell *bar1* mutants lacking barrier produce unusual wrinkled colonies, and that these colonies are responding to pheromone. They also discovered, surprisingly, that **a**-**a** cell fusion can occur both between *bar1* mutants and between wild-type and *bar1* mutant cells. Crosses with mutant strains showed that same-sex mating occurs when α -pheromone is produced by one **a**-cell and is sensed by α -pheromone receptors on both the producing and the partner **a**-cell.

Alby *et al.* found that same-sex mating is less efficient than opposite-sex mating, but is readily detectable, and in some cases is appreciable. They also observed same-sex mating between wild-type **a**-cells (producing Bar1) in ménage a trois matings in which an α -cell minority provided α -pheromone. Under these conditions, sufficient α -pheromone may overwhelm Bar1 and trigger **a**-**a** cell fusion. Same-sex mating yielded tetraploid cells (**a/a/a/a**) that could undergo parasexual chromosome loss to diploid progeny. Thus, both mating-type locus versions are not needed for the parasexual cycle, in contrast to their requirement for meiosis in *S. cerevisiae*.

Do opposite- and same-sex mating occur in nature? The original discovery of inefficient *C. albicans* **a**- α mating fuelled speculation it could be a lab artefact, yet a complex cellular network has been maintained that supports efficient **a**- α mating. Population genetic studies and identification of mating-stimulatory host conditions lend further support to the view that opposite-sex mating happens in nature²⁻⁴. That same-sex mating occurs most efficiently with mutant and not wild-type strains suggested *bar1* mutants might occur in the population. No natural *bar1* mutants have been identified thus far, however, and they might arise only transiently. Alternatively, host conditions or protease inhibitors produced by *C. albicans* (α -pheromone variants) might stimulate same-sex mating in nature. Even infrequent same-sex mating in ménage a trois matings might suffice for genetic exchange in skewed mating-type populations, such as commensal biofilms on host mucosal membranes.

Although it might seem odd that yeast would mate by both opposite-sex/out-crossing and same-sex/inbreeding, *S. cerevisiae* is again instructive. The natural population consists of isolates that switch mating-type and self-mate, and others that cannot switch but are fertile with the opposite mating-type. Thus, a well-defined species can evidently consist of individuals with different modes of sexual reproduction. It is striking, however, that two closely related yeasts (*C. albicans* and *S. cerevisiae*) evolved such distinct modes of self-fertility. The more evolutionarily divergent fission yeast, *Schizosaccharomyces pombe*, also switches mating-type and self-mates, like *S. cerevisiae*, but independently evolved a machinery to do so. This diversity in forms of sexual reproduction illustrates the remarkable plasticity of fungi as they have evolved to exploit different environments.

A divergent pathogenic yeast, *Cryptococcus neoformans*, also reproduces unisexually⁸. This species has a well-defined **a**- α sexual cycle, and it was puzzling why the natural population is largely α unisexual. The discovery that α cells undergo same-sex mating, yielding diploid cells that complete meiosis and produce spores (Fig. 2), suggested another route by which diversity might be maintained⁸. Population genetics studies provide evidence that same-sex mating occurs in nature, and implicate the process in an outbreak of *Cryptococcus* infection^{9,10}. That same-sex mating arose convergently in two divergent pathogenic yeasts suggests unisexual reproduction may be linked to microbial pathogenesis, and could be even more widespread than currently appreciated.

Transitions in sexual reproduction between inbreeding and out-breeding also occur in plants and animals. In plants, mutations in self-incompatibility loci involved in pollen recognition evoke transitions from cross-pollination to self-pollination¹¹. One individual can thereby

colonize different environmental niches, and become more cosmopolitan. Parthenogenesis — ‘virgin birth’ — is restricted in mammals by genomic imprinting, but remarkable examples have been reported in Komodo dragons and sharks^{12,13}. In these cases, otherwise sexual organisms reproduce under extreme circumstances, possibly enabling the colonization of islands or oceanic expanses by single individuals.

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Figure 1. Opposite-sex and same-sex mating in *Candida albicans*

This fungus is diploid ($2n$): most strains are heterozygous, having both mating-type gene forms (a/α), and are sterile. **a**, Opposite-sex mating involves loss of heterozygosity, yielding a and α diploid cells that then switch from the white type to the opaque type specialized for mating. Cell-cell fusion yields tetraploid ($4n$) cells in which parasexual chromosome reduction without recognized meiosis yields diploid progeny. **b**, Same-sex mating again involves loss of heterozygosity and the white–opaque switch. As identified by Alby *et al.*¹, the same-sex path can then be advanced in two ways, both of which involve production of pheromone of the opposite mating type that promotes fusion and results in a tetraploids. If a -cells lack Bar1 protease, they do not destroy the α -pheromone they produce; and in ménage a trois matings, even a few α -cells can provide α -pheromone.

A Same sex mating in *Candida albicans*

B Same sex mating in *Cryptococcus neoformans*

Figure 2. Same-sex mating in two pathogenic fungi

Unisexual reproduction occurs in both *Candida albicans* (a) and *Cryptococcus neoformans* (b). These forms of self-fertility may result in population features (inbreeding, clonality) that are associated with pathogenesis. Given that two such evolutionarily diverged pathogenic fungi both undergo same-sex mating, this process is likely to be even more general among fungi. The two species are distinguished in that mating in *C. albicans* is parasexual and no spores are produced, whereas in *C. neoformans* meiosis results in the production of infectious spores.