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REVIEW

Regulation of white-opaque switching in *Candida albicans*

Joachim Morschhäuser

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Abstract The yeast *Candida albicans* is part of the microflora in most healthy people, but can become a pathogen when host defenses are compromised. The phenotypic plasticity of *C. albicans*, which includes switching between different morphologies, contributes to its ability to colonize and infect virtually all body locations. A particularly fascinating developmental program is white-opaque switching, a reversible transition between the normal yeast morphology (white) and an elongated cell type (opaque), which is the mating-competent form of this fungus. Although opaque cells are much less able than white cells to cause a systemic infection, they are better adapted for colonization of specific host niches, like skin. White-opaque switching is controlled by the mating type locus (*MTL*), which in most *C. albicans* strains exists in two alleles, *MTL***a** and *MTL*α. These strains produce a heterodimeric repressor, **a**1-α2, which suppresses switching to the opaque phase by inhibiting expression of the master regulator Wor1. Loss of *MTL* heterozygosity relieves this repression, a mechanism that ensures that only *MTL* homozygous cells can switch to the mating-competent opaque form. Several transcriptional feedback loops, including positive autoregulation of Wor1, result in bistable expression of the master regulator (low in white and high in opaque cells) and epigenetic inheritance of the two phases. White-opaque switching occurs stochastically at a low frequency, but certain environmental conditions can drive the switch from one phase to the other by affecting either the activity of the transcriptional feedback loops or accumulation of Wor1 protein in a cell. Such environmental regulation of phenotypic switching may restrict mating to suitable host niches, while allowing a *C. albicans* population to withstand the various challenges encountered in different tissues.

Keywords Phenotypic switching · Mating · Transcriptional regulation · Epigenetic control

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J. Morschhäuser (✉)
Institut für Molekulare Infektionsbiologie, Universität Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg, Germany
e-mail: joachim.morschhaeuser@mail.uni-wuerzburg.de

Introduction

The yeast *Candida albicans* is usually a harmless commensal microorganism that lives on the gastrointestinal and urogenital mucosa of most healthy persons. However, especially in immunocompromised patients, *C. albicans* can become a pathogen and cause superficial as well as life-threatening systemic infections [1]. Many phenotypic attributes of *C. albicans* contribute to its capacity to colonize and infect virtually all body locations. The ability to adhere to many different tissues enables efficient colonization of a variety of host niches, and the metabolic flexibility of the fungus allows it to utilize the nutrients that are available at these sites [2, 3]. Another important adaptation mechanism is the morphological versatility of this pathogen. *C. albicans* does not only grow as a budding yeast, but can also switch to filamentous growth forms, including true hyphae and pseudohyphae. Filamentous growth, which is controlled by environmental conditions, is important for tissue invasion and strongly linked to the virulence of the fungus [4].

Candida albicans can also spontaneously and reversibly switch from the normal, round-to-oval yeast form to an elongate or bean-shaped cell type that also proliferates by

budding (Fig. 1a). This phenotypic transition, which was discovered in 1987 [5], was termed white-opaque switching because of the appearance of the colonies produced by the two cell types on solid media. White cells form hemispherical, white colonies, whereas opaque cells form flat, gray colonies that can be selectively stained red with phloxine B (Fig. 1b). It is now known that opaque cells are the mating-competent form of *C. albicans* and only cells that are homozygous at the mating type locus can switch from the white to the opaque phase and mate with other opaque cells to generate recombinant progeny [6, 7]. This review summarizes our current knowledge about the regulation of white-opaque switching and its implications for the interaction of *C. albicans* with its mammalian host.

White-opaque switching as a host adaptation mechanism

The white and opaque phases of switching-competent strains differ not only in their cell and colony morphologies, but also in their gene expression patterns. After the initial discovery of individual white- and opaque-specific genes [8–10], which are exclusively expressed in the respective cell type (Fig. 2), subsequent genome-wide gene expression analyses showed that under identical growth conditions

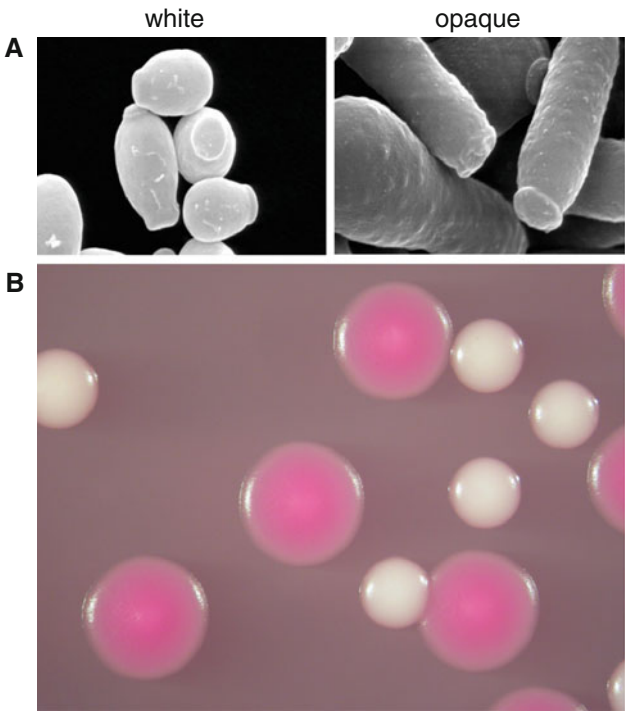

Fig. 1 **a** Scanning electron micrographs of white and opaque cells of *C. albicans*. Note the characteristic pimples on the surface of the elongate opaque cells. **b** Colonies formed by white and opaque cells on an agar plate containing phloxine B, which selectively stains opaque colonies *red*. Pictures were taken from references [54] and [55]

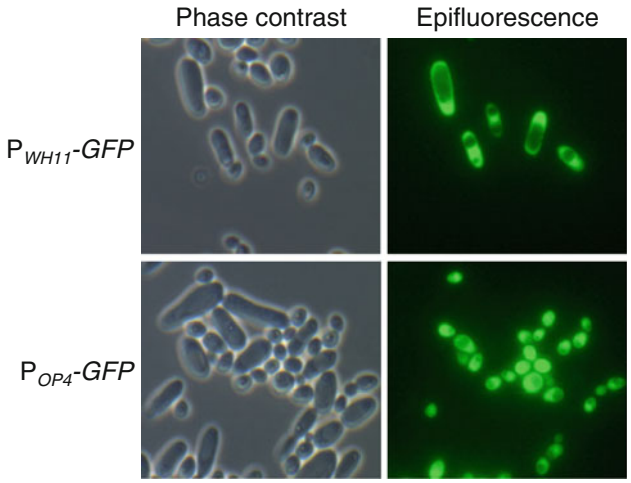

Fig. 2 Phase-specific gene expression in white and opaque cells. White and opaque cells of strains expressing green fluorescent protein (GFP) from the promoter of the white-specific *WH11* gene (P_{WH11}-*GFP*) or the opaque-specific *OP4* gene (P_{OP4}-*GFP*) were mixed and visualized by fluorescence microscopy. Pictures were taken from references [56]

several hundred genes are differentially expressed in white and opaque cells [11, 12]. Some of these genes are related to the mating process, e.g., genes encoding proteins involved in pheromone production, sensing, and response. However, many of the differentially expressed genes have functions that are not related to mating, suggesting that they confer specific characteristics upon the two cell types that facilitate adaptation to certain host niches.

Candida albicans possesses many different cell surface adhesins and some of these are expressed at higher levels in white cells, while others are upregulated in opaque cells [12]. This indicates that the two cell types may preferentially colonize different tissues. Indeed, white cells adhere better than opaque cells to human buccal epithelial cells [13]. Conversely, opaque cells are better colonizers of the skin, which is an environment that highly facilitates mating of these cells [14, 15]. Although opaque cells are capable of forming hyphae, they do not undergo the yeast-hyphal switch under many conditions that efficiently stimulate hyphal growth in white cells [16]. Therefore, by forming hyphae, cells in the white phase may invade tissue barriers more readily than cells in the opaque phase. White and opaque cells also differ in their metabolic capacities. Approximately one-third of the genes that are differentially regulated in the two cell types are related to metabolism, pointing to a metabolic specialization of the switch phenotypes [12]. For example, opaque cells cannot assimilate certain sugars that are metabolized by white cells [17]. Such differences could affect the ability of the cells to utilize nutrients that are available in various host niches.

White-opaque switching may also allow an escape from certain host defense mechanisms. An early study reported

that white and opaque cells were phagocytosed with equal efficiency by polymorphonuclear leukocytes (PMNs), but white cells were more resistant to killing by these cells [18]. Opaque cells were also found to be more sensitive than white cells to reactive oxygen species, which are produced by host phagocytic cells to kill pathogenic microorganisms. On the other hand, it was observed that white cells, but not opaque cells, release a chemoattractant for PMNs, indicating that opaque cells have developed mechanisms to avoid recognition by these primary host defense cells [19]. Another recent study showed that opaque cells are much less efficiently phagocytosed than white cells by two different types of innate immune cells, *Drosophila* S2 cells and a mouse macrophage-derived cell line [20]. Therefore, white-opaque switching may allow *C. albicans* to escape or withstand specific components of the host immune system.

The phenotypic differences between white and opaque cells are reflected by differences in the relative virulence of the two cell types. After intravenous infection of mice with cells in the opaque phase, much fewer cells were recovered from the kidneys, the main target organ in this infection model, than after infection with white-phase cells [21]. In addition, most of the recovered cells had switched from the opaque to the white phenotype, indicating that opaque cells are less able than white cells to cause a disseminated infection and switching from the opaque to the white phase may confer a selective advantage under these conditions. On the other hand, as mentioned above, in a mouse model of cutaneous infection opaque cells colonized the skin much more efficiently than did white cells, and phase-specific expression of a secreted protease contributed to the increased virulence of opaque cells in this infection model [14]. Thus, depending on the host niche, the white or opaque phenotype can be advantageous for colonization and/or infection.

Genetic control of white-opaque switching

Candida albicans is a diploid species without a known haploid phase, and white-opaque switching occurs only in strains that are homozygous at the mating type locus (*MTL*). The majority of *C. albicans* strains found in nature contain two different *MTL* alleles, *MTL***a** and *MTL*α, and produce a heterodimeric repressor formed by the homeodomain proteins **a**1 (encoded by *MTL***a**) and α2 (encoded by *MTL*α), which suppresses switching to the opaque phase [6, 11]. However, heterozygous *MTL***a**/*MTL*α cells (**a**/α cells) can become homozygous for *MTL***a** (**a** cells) or *MTL*α (α cells). This loss of heterozygosity occurs either by mitotic recombination or by loss of one copy of chromosome 5, which contains *MTL*, and duplication of the other chromosome 5 homologue [22, 23]. Such cells cannot produce the **a**1-α2 repressor any more and are switching-competent. After mating of opaque **a** and α cells, the resulting tetraploid cells produce the repressor again and switch back to the white phase. The cells can remain tetraploid or return to the diploid state by a non-meiotic parasexual program of random, yet concerted, chromosome loss [24].

White-opaque switching in *MTL* homozygous strains does not involve genomic alterations. Instead, it is controlled by an epigenetic mechanism that is based on the activity of the transcription factor Wor1 (white-opaque regulator 1), the master regulator of white-opaque switching [25–27]. *WOR1* expression is suppressed by the **a**1-α2 repressor, which explains why **a**/α cells cannot switch to the opaque phase. In cells that have become *MTL* homozygous, *WOR1* is relieved from repression by **a**1-α2. In the white phase, **a** and α cells still express *WOR1* at very low levels, but a stochastic increase in the amount of Wor1 above a threshold level in some cells of a population induces these cells to switch to the opaque phase. Wor1 binds to the *WOR1* promoter and activates its own expression, resulting in a positive feedback loop that provides the high Wor1 levels required for switching to and maintaining the opaque phenotype (Fig. 3). Wor1 also binds to the promoters of many other genes and presumably regulates their expression in opaque cells [28]. Mutants lacking *WOR1* are locked in the white phase and cannot undergo white-opaque switching. Conversely, transient ectopic expression of Wor1 is sufficient to activate the positive autoregulatory loop and promote switching to the opaque phase, which is then stably maintained until a decrease in Wor1 levels in a cell destabilizes the opaque phase and allows switching to the white phase. The bistable expression of Wor1 explains both the stochastic nature of white-opaque switching and the heritability of the white and opaque phenotypes.

Additional regulatory mechanisms ensure the stability of the white and opaque phases. The zinc cluster transcription

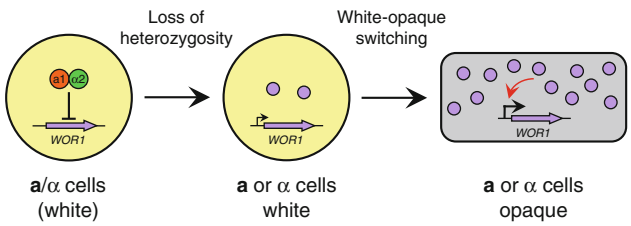

Fig. 3 Control of white-opaque switching by the mating type locus and the master regulator Wor1. *MTL* heterozygous cells produce the **a**1-α2 repressor, which inhibits expression of the *WOR1* gene, and cannot switch to the opaque phase. Loss of *MTL* heterozygosity generates **a** or α cells, in which *WOR1* repression by **a**1-α2 is relieved. In the white phase, these cells express Wor1 at very low levels, but a stochastic increase in the amount of Wor1 in some cells of a population induces switching to the opaque phase. Positive autoregulation of Wor1 ensures continued high Wor1 expression and stable inheritance of the opaque state. Adapted from reference [27]

factors Czf1 and Wor2 are positive regulators of white-opaque switching that are upregulated in opaque cells [28–30]. Overexpression of Czf1 promotes Wor1-dependent switching from the white to the opaque phase, but once the opaque state is established, Czf1 is no longer essential for its maintenance. In contrast, cells lacking *WOR2* can only be switched to the opaque phase upon ectopic expression of *WOR1* and rapidly revert to the white phase when the ectopic *WOR1* copy is shut off, demonstrating that Wor2 is required for the stability of the opaque phase [28]. The basic helix-loop-helix transcription factor Efg1 is a negative regulator of white-opaque switching that is downregulated in opaque cells. It promotes switching from opaque to white and is required for maintenance of the white phase [28, 31, 32]. Therefore, cells lacking *EFG1* exist almost exclusively in the opaque phase, but only when *WOR1* and *WOR2* are present, further underlining the essentiality of the master regulator Wor1 for establishing the opaque state [28, 33].

Based on the phenotypes of strains lacking or overexpressing the transcriptional regulators of white-opaque switching and on DNA binding and genetic interaction studies, the model depicted in Fig. 4 for control of white-opaque switching was proposed [28]. Wor1, together with the coregulator Mcm1 [34] (not shown in the figure), binds to its own promoter as well as those of *CZF1*, *WOR2*, and *EFG1*. By stimulating expression of *WOR1*, *WOR2*, and *CZF1* and repressing *EFG1* expression in opaque cells, Wor1 ensures stable maintenance of the opaque phase. In white cells, repression of *EFG1* by Wor1 does not occur and Efg1 can, in turn, repress *WOR1* expression and thereby inhibit switching to the opaque phase. In this model, Wor2 directly promotes *WOR1* activity, whereas the regulation by Czf1 and Efg1 is indirect: Czf1 inhibits the negative regulator Efg1, and Efg1 represses the positive regulator *WOR2*. The positive transcriptional feedback loops are active in the opaque state and interrupted in the white state and are responsible for the heritability of the white and opaque phases and the frequency of switching between them.

As mentioned above, repression of *WOR1* expression by the **a**1-α2 repressor blocks white-opaque switching in **a**/α cells. Forced expression of *WOR1* from a heterologous promoter in **a**/α cells induces white-opaque switching, but the opaque cells are unable to mate because genes required for mating are still repressed by the **a**1-α2 repressor [25]. In contrast, overexpression of *CZF1* in **a**/α cells does not promote white-opaque switching, because Czf1 cannot overcome the repression of *WOR1* by the **a**1-α2 repressor [30]. Similarly, deletion of *EFG1* in **a**/α cells does not result in switching to the opaque phase because *WOR1* remains repressed in these cells [28].

Chromatin modifications also affect the frequency of switching between the white and opaque phases. Inhibition

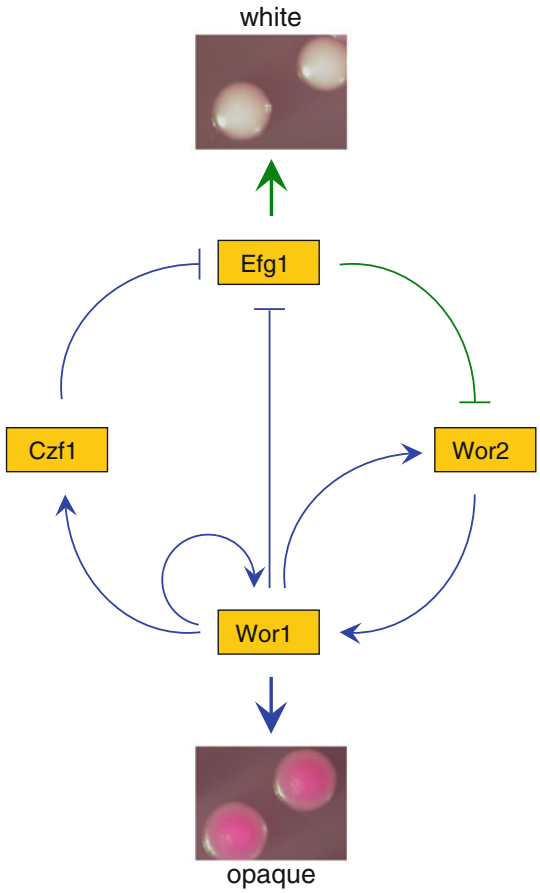

Fig. 4 Model of transcriptional regulation of white-opaque switching by Wor1, Wor2, Czf1, and Efg1. *Lines* with *arrows* indicate activation and *lines* with *bars* indicate repression. Activities that dominate in white and opaque cells are marked in *green* and *blue*, respectively. Adapted from reference [28]

of histone deacetylation with trichostatin A or deletion of the histone deacetylase encoding gene *HDA1* strongly stimulated switching from white to opaque, while deletion of *RPD3*, encoding another histone acetylase, increased the frequency of switching in both directions [35, 36]. *EFG1* expression is strongly reduced in white cells of the *hda1* mutant, which could explain the increased switching to the opaque phase in cells lacking Hda1. Expression of *HDA1* itself and other histone deacetylases was also found to be downregulated in opaque cells [36]. Additional histone-modifying enzymes affect the frequency of white-opaque switching, and deletion of the corresponding genes increases or decreases switching in one or the other direction [33]. Interestingly, *efg1*Δ mutants, which exist almost exclusively in the opaque state, could switch to the white phase at wild-type rates after inactivation of the Set3 histone deacetylase complex, indicating that derepression of *WOR1* in the absence of Efg1 requires the activity of this histone deacetylase. No differential expression of the histone deacetylases in white and opaque cells was observed

in the latter study and it was suggested that the activities rather than the expression levels of histone modifiers modulate the transcriptional regulatory circuit that controls switching.

An interesting twist to the control of white-opaque switching came from the observation that deletion of one allele of the essential *HBR1* gene, whose expression is increased in the presence of hemoglobin, enabled heterozygous **a**/α cells to switch to the opaque phase at a frequency similar to that seen in *MTL* homozygous cells [37]. Expression of the *MTLα1* and *MTLα2* genes was abolished in the *HBR1*/*hbr1* mutants, such that they behaved like **a** cells and, when in the opaque phase, were able to mate with opaque α cells. How Hbr1 controls *MTLα1* and *MTLα2* expression is unclear, but these findings suggest that down-regulation of *HBR1* expression might allow white-opaque switching to occur also in **a**/α cells. However, so far white-opaque switching has not been observed under any tested conditions (usually in the absence of hemoglobin) in natural *C. albicans* **a**/α strains without previous loss of *MTL* heterozygosity [7, 38].

Environmental regulation of white-opaque switching

White-opaque switching is a stochastic process that occurs approximately every 10^3–10^4 generations, resulting in semistable maintenance of the two phases. However, the frequency of switching in either direction is modulated by environmental conditions, indicating that the activity of components of the regulatory feedback loops that ensure epigenetic inheritance of the white and opaque phases can be changed by specific signals.

White-opaque switching is stimulated ca. 10- to 20-fold in both directions by low doses of UV irradiation [39]. While neutrophils and oxidants promote switching from white to opaque [18], both decreased (4°C) and increased temperature (37°C) strongly stimulate opaque cells to switch to the white phase, the latter resulting in mass conversion to the white cell phenotype [5, 40, 41]. It is not known by which mechanisms these environmental conditions affect the frequency of switching, but they must somehow, directly or indirectly, alter the Wor1 levels in individual cells to induce switching to the opposite phase. It was recently shown that some stress conditions, including genotoxic and oxidative stress, promote the switch from white to opaque by slowing growth of the cells without affecting their metabolic activity, which allows Wor1 to accumulate before cell division and induce switching [42].

The fact that the mammalian body temperature promotes mass switching of opaque cells to the white phase is in line with the finding that mostly white cells were recovered from the kidneys of mice that were intravenously infected with opaque cells [21]. This indicated that opaque cells would be stable only in an environment with a lower temperature, like the surface of the skin, which is colonized more efficiently by opaque than by white cells [14]. It was also suggested that skin is more likely to be colonized by multiple *C. albicans* strains, which would increase the chances that strains of opposite mating type encounter one another and mate after switching to the opaque phase [43].

In our own work, we recently discovered that a transient incubation of white cells of the *MTLα* strain WO-1 under anaerobic conditions resulted in mass-switching of the cells to the opaque phase [29]. The induction of white-opaque switching by anaerobic conditions occurred with high efficiency also at 37°C, a temperature that normally stimulates the reverse transition from opaque to white. These findings suggested that switching to the opaque phase may be induced in appropriate niches also within the mammalian body. Indeed, after passage of white cells of strain WO-1 through the gastrointestinal tract of mice, where anaerobic conditions are likely to be encountered, a significant proportion of cells that were recovered from the feces of the animals had switched to the opaque phase. In the absence of oxygen, ergosterol biosynthesis is inhibited, and yeast cells may sense anaerobic conditions by the resulting ergosterol depletion [44]. In line with this, treatment of white cells of strain WO-1 with ergosterol biosynthesis inhibitors also induced switching to the opaque phase [29]. The induction of white-opaque switching in an anaerobic environment required the transcription factor Czf1, which induces filamentous growth in **a**/α strains when the cells are embedded in a matrix [45], conditions in which oxygen presumably becomes depleted during growth. Anaerobic conditions may therefore activate the transcriptional feedback loop that stimulates white-opaque switching by increasing the activity of Czf1 (see Fig. 4). Interestingly, we did not observe anaerobic induction of white-opaque switching in several other switching-competent strains, and these strains did also not switch to the opaque phase after passage through the mouse gastrointestinal tract [29]. This indicates that *C. albicans* strains may differ in their response to environmental conditions that stimulate switching to the mating-competent opaque phase.

Under anaerobic conditions, opaque cells do not revert to the white phase at 37°C and can mate with high efficiency [46]. This finding suggested that opaque cells may be sufficiently stable in anaerobic niches within the host for successful mating to occur. In support of this hypothesis, recombinant mating products have been recovered from the colon and cecum of mice that were infected in turns with **a** and α opaque cells in their drinking water [46].

Elevated CO_2 concentrations have also been shown to strongly induce white-opaque switching and stabilize the

opaque phase at 37°C in all switching-competent strains tested [47]. It is likely that elevated CO_2 concentrations also contributed to the induction of white-opaque switching observed under anaerobic conditions in strain WO-1 [29]. *C. albicans* **a**/α strains sense intracellular CO_2 via adenylyl cyclase to induce filamentous growth [48]. Yet, high CO_2 concentrations efficiently stimulated white-opaque switching in an *MTL***a** strain lacking adenylyl cyclase, demonstrating that *MTL* homozygous strains must use an additional CO_2 sensing mechanism to promote switching of white cells to the opaque phase in response to this environmental cue [47]. In contrast to anaerobic conditions, high CO_2 concentrations strongly stimulated white-opaque switching also in a *czf1*Δ mutant, albeit not as efficiently as in the wild-type parental strain [47]. As mammalian tissues contain high CO_2 concentrations, this physiological signal could enable white-opaque switching, prolonged maintenance of the opaque phase, and mating of *MTL* homozygous strains in many different host niches. But, as mentioned above, opaque cells usually switch to the white phase during systemic infection of mice, indicating that the temperature signal or other conditions may often override the CO_2 signal [21]. White cells also remained stable and did not switch to the opaque phase when incubated in the presence of elevated CO_2 concentrations in liquid medium [47]. It is likely that the relative strength and duration of opposing environmental signals (e.g., anaerobic conditions/high CO_2 concentrations versus physiological temperature) determine whether white-opaque switching and mating can occur in a given body location. Mating products have been isolated from the kidneys of mice infected with **a** and α cells in the white phase [49], supporting the idea that appropriate conditions in certain host niches can stimulate white cells to switch to the mating-competent opaque phase also at body temperature.

Conclusions

White-opaque switching is a unique developmental program that is required for mating in *C. albicans* (and the closely related species *C. dubliniensis*) but does not exist in other fungi. The natural habitat of *C. albicans* is humans and warm-blooded animals [1] and it is generally assumed that the inclusion of white-opaque switching as an additional step in the mating process is a consequence of the coevolution of *C. albicans* with its host [50–52]. White and opaque cells differ in their abilities to colonize and infect specific host tissues. The stochastic nature of switching ensures that a population of white or opaque cells contains a minor proportion of cells in the opposite phase, which may be better adapted to a new host niche or to alterations in the environment [17]. Opaque cells are usually less virulent than white cells and also more susceptible to many adverse conditions. Therefore, this mating-competent cell form probably survives and propagates only in specific, favorable body locations. The finding that switching to the opaque phase can be strongly stimulated by certain environmental signals suggests that switching-competent strains can also react to the presence of a suitable environment by switching. Interestingly, opaque cells can boost biofilm formation by white cells of the opposite mating type [53]. This suggests that the formation of opaque cells does not only allow mating, which occurs with higher efficiency in a thick biofilm, but may also enhance the ability of a mixed population of white and opaque cells of opposite mating types to persist in infected tissue [52]. Clearly, much remains to be learned about the role of white-opaque switching in the adaptation of *C. albicans* to its mammalian host.

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