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Candida albicans the chameleon: transitions and interactions between multiple phenotypic states confer phenotypic plasticity

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Abstract

The ability of microbial cells to exist in multiple states is a ubiquitous property that promotes adaptation and survival. This phenomenon has been extensively studied in the opportunistic pathogen *Candida albicans*, which can transition between multiple phenotypic states in response to environmental signals. *C. albicans* normally exists as a commensal in the human body, but can also cause debilitating mucosal infections or life-threatening systemic infections. The ability to switch between cellular forms contributes to *C. albicans*' capacity to infect different host niches, and strictly regulates the program of sexual mating. We review the unique properties associated with different phenotypic states, as well as how interactions between cells in different states can further augment microbial behavior.

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The white-opaque switch governs multiple aspects of *Candida albicans* biology

C. albicans exists as a harmless commensal in the gastrointestinal tract and is also commonly isolated from the skin and oral cavity of healthy individuals [1]. However, it can transition to an infectious colonizer of virtually any organ in the body, particularly in immunocompromised patients. *C. albicans* is currently the most common cause of life-threatening fungal infections in these individuals, with an estimated mortality rate of 46–75% [2,3].

C. albicans exhibits several forms of phenotypic switching in which cells undergo a reversible and heritable transition between alternative cell states. The best characterized of these epigenetic transitions is the white-opaque switch, named for the appearance of colonies on agar media. White cells are round and form brighter, dome-shaped colonies, whereas opaque cells are elliptical and form flatter, duller colonies [4]. Miller and Johnson demonstrated that the switch to the opaque state is necessary for efficient sexual mating [5••], stimulating interest into how phenotypic diversity impacts important physiological traits in *C. albicans*. Although refractory to mating, white cells were subsequently shown to respond to mating pheromones resulting in 'sexual' biofilms [6••], as further discussed below. White and opaque states exhibit many other distinct properties as outlined in Table 1. For example, white cells are predicted to have a fermentative metabolism, whereas opaque cells express genes associated with an oxidative metabolism [7]. Opaque cells are better colonizers of the skin, whereas white cells are more virulent in a bloodstream model of infection [8,9]. Furthermore, white cells are more susceptible to phagocytosis by host macrophages [10] and secrete a leukocyte chemoattractant [11], whereas opaque cells do not. These findings raise the possibility that the switch to the opaque state could promote immune evasion, although opaque cells are also more sensitive to reactive oxygen species, a common defense mechanism of host phagocytes [12].

Regulation of phenotypic switching

C. albicans strains are typically isolated in the white phenotypic state, in which the regulatory circuit is dependent on the transcription factor Efg1 [13–15]. Conversely, expression of the Wor1 transcription factor is necessary and sufficient for stable transitioning to the opaque state [16–18]. Wor1 acts in concert with at least five other transcription factors as part of a network of positive and negative feedback loops to regulate bi-stability in *C. albicans* [15,19]. Chromatin-level changes control the switching frequency, including a role for hyperacetylation of histone H3K56 in promoting opaque cell formation [20–23] and deposition of H2A.Z in promoting the white state [24]. Mediator complex also regulates white-opaque switching, as deletion of certain mediator components can destabilize the white or opaque states [25]. More recently, experiments demonstrated that the long 5′ untranslated region (5′ UTR) of *WOR1* regulates switching by reducing translational efficiency on the *WOR1* transcript [26]. These experiments reveal complex transcriptional, post-transcriptional and chromatin-mediated regulation of the switch, with parallels to

Table 1

Characteristic properties of the heritable cell states in *C. albicans*. Cells in each state have unique phenotypic properties. *MTL*, mating-type locus. Predicted metabolic preferences based on gene expression studies.

State	*MTL* configuration	Major regulator	Cues supporting formation of each state	Metabolism	Preferred niche	Pheromone response
White	Heterozygous or homozygous	Efg1 [13,14,19]	Stable at 25 °C or 37° C [35], aerobic conditions [37]	Fermentative [7]	Commensal, bloodstream [8]	Biofilm formation [6••]
Opaque	Usually homozygous [5••,28] but can be heterozygous [30]	Wor1 [16–18]	25 °C [35], CO_2 [36], anaerobiosis [37], N-acetyl glucosamine [38]	Oxidative [7]	Skin [9]	Mating [5••]
Gray	Heterozygous or homozygous [44••]	N/A	Stable at 25 °C or 37 °C on rich media (YPD) [44••]	Unique carbohydrate metabolism [44••]	Skin [44••]	Mating at low efficiency [44••]
GUT	Heterozygous [45•]	Requires Wor1 over-expression [45•]	Passage through the mammalian gastrointestinal tract [45•]	Adapted to the gastrointestinal tract, high iron [45•]	Commensal in gastrointestinal tract [45•]	No response [45•]

other heritable circuits including embryonic stem cell differentiation [27].

The white-opaque switch is also controlled by transcription factors encoded at the *MTL* (mating-type locus). Switching from white to opaque typically requires that diploid strains are homozygous at this locus (*i.e.*, either '*MTL***a**/**a**' or '*MTL*α/α') [5••,28], as expression of Wor1 is repressed by a complex of **a**1 and α2 transcription factors that is present in *MTL***a**/α cells [29]. However, recent work has shown that certain **a**/α isolates can also switch to the opaque state under specific environmental conditions [30]. A similar white-opaque switch has been discovered in the related species *Candida tropicalis* [31••,32] and *Candida dubliniensis* [33]. In the case of *C. tropicalis*, white-opaque switching appears to be independent of *MTL* regulation [32,34]. The fact that the switch exists exclusively in three commensal fungi that co-evolved with the mammalian host suggests that this transition provides an advantage for survival *in vivo*.

Multiple environmental factors influence *C. albicans* switching between white and opaque states. Conditions that affect switching *in vitro* include temperature [35], carbon dioxide [36], anaerobiosis [37], N-acetylglucosamine [38] and genotoxic and oxidative stress [39]. *In vivo*, opaque-to-white switching occurs *en masse* during systemic infection [40], whereas increased switching in the opposite direction, from white to opaque, was observed in one strain during gastrointestinal colonization [41]. The sensitivity of the switch to a diverse array of environmental factors is reflective of multiple pathways impinging on white-opaque signaling. Some of these have been defined and include the pheromone MAPK cascade [42••], the cAMP/PKA pathway [38], and the Hog1 stress-activated protein kinase pathway [43].

Recently, *C. albicans* was shown to stably exist in two additional phenotypic states, termed the 'gray' and 'GUT' states, that are related to white and opaque forms (Figure 1). Gray cells displayed a distinct metabolic profile from white and opaque cells, and were more successful than either of these states in an *ex vivo* mouse tongue infection model [44••]. Cells in the GUT state were observed following gastrointestinal colonization using a strain that overexpressed the *WOR1* gene [45•]. GUT cells were hypercompetitive when re-tested in this niche, indicating a potential role for this phenotypic state in promoting commensalism [45•]. The metabolic reprogramming of cells can therefore generate specialized forms that enable colonization and infection of different host niches.

C. albicans mating necessitates switching to the opaque state

The most striking difference between white and opaque cells is their sexual fecundity. Opaque cells are the mating competent form of *C. albicans*, mating a million times more efficiently than white cells [5••]. Conventional heterothallic mating occurs between diploid **a** and α opaque cells and is driven by the secretion and response to sex-specific pheromones (Figure 2A). A conserved MAPK cascade transduces the pheromone signal resulting in activation of the transcription factor Cph1 (ortholog of *Saccharomyces cerevisiae* Ste12). This triggers polarized growth, cell fusion and karyogamy, resulting in the formation of tetraploid mating products [46–49]. Meiosis has not been observed in *C. albicans* and instead tetraploid cells return to the diploid state by a series of reductional mitotic divisions [50–52]. It was revealed that *C. albicans* diploid cells can reduce their ploidy to that of true haploids by a similar parasexual process, further extending the range of ploidy states that can be adopted by this species (also see Gerstein and Berman review, this issue).