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Fungal interactions with the human host: exploring the spectrum of symbiosis

Rebecca A Hall^{1,3} and Mairi C Noverr^{2,3}

Fungi are ubiquitous transient or persistent human colonisers, and form the mycobiome with shifts in niche specific mycobiomes (dysbiosis) being associated with various diseases. These complex interactions of fungal species with the human host can be viewed as a spectrum of symbiotic relationships (i.e. commensal, parasitic, mutualistic, amensalistic). The host relevant outcome of the relationship is the damage to benefit ratio, elegantly described in the damage response framework. This review focuses on *Candida albicans*, which is the most well studied human fungal symbiont clinically and experimentally, its transition from commensalism to parasitism within the human host, and the factors that influence this relationship.

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Introduction

Fungi are ubiquitous within the environment. However, only a few species are routinely found associated with humans and are capable of causing disease. A handful of these fungi are considered true pathogens, causing disease in healthy individuals (*Histoplasma* and *Paracoccidioides*), while the majority of fungi are often classified as opportunistic pathogens (i.e. *Candida* and *Cryptococcus*), causing disease primarily in immunosuppressed individuals [1]. However, it is apparent that some opportunistic fungal pathogens also cause disease in otherwise healthy individuals (i.e. *Candida* vaginitis or *Cryptococcus gattii* outbreaks) [2,3]. To understand and categorize the complexity of these different interactions between host and pathogen, Casadevall and Pirofski proposed the damage

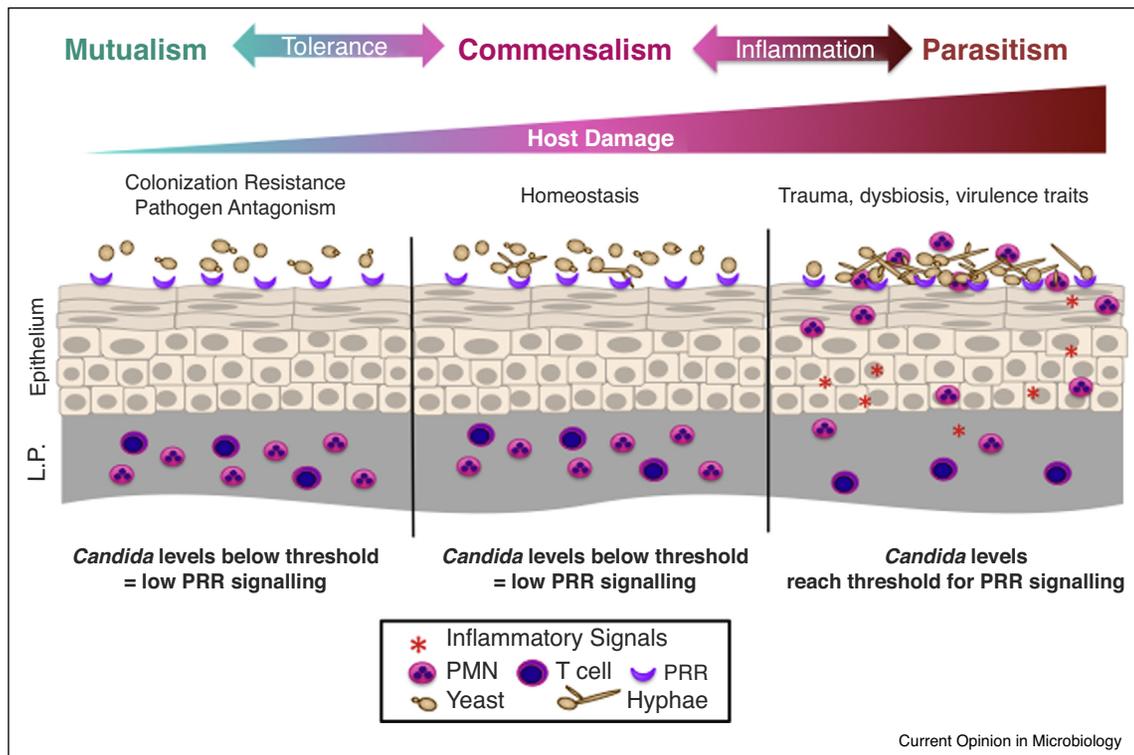
response framework (DRF), which defines microbial virulence as a function of host damage [4]. Within this framework, host damage (and therefore disease) can occur at either end of the host immune response spectrum (i.e. weakened or hyperactive immune defences). Along this spectrum there is a continuum between pathogen-mediated and host-mediated damage, which results in disease only when damage impairs the normal function of the host.

Host damage also varies as a function of time, with several possible outcomes of host–pathogen interactions. For example, as the amount of damage increases over time and surpasses a threshold, disease ensues [4]. Fungal pathogens that are able to exist within the host for extended periods of time with limited damage lead to other outcomes, including latency (*Cryptococcus*) or commensalism. In addition, many fungal pathogens cause chronic (long-term) infections, and therefore could also be classified as symbionts, albeit with different host/microbe damage to benefit ratios. The most well studied fungal commensal is *Candida albicans*, which colonises the oral, genital and gastrointestinal tracts, but can cause host damage and disease in the context of weakened or uncontrolled immune responses. An environmental reservoir of *C. albicans* has not yet been identified. Therefore, *C. albicans* is considered an obligate commensal fungus. This and its ability to fit within all six classes of the DRF [5^{*}] have made *C. albicans* the model fungus for studying the transition from commensal to pathogen and will be the main focus of this review.

Symbiosis within the human ecosystem

Symbiosis is a type of long-term close biological relationship between two or more species. These relationships can be mutualistic (all organisms benefit), commensalistic (one organism benefits without affecting the other), parasitic (one organism benefits at the expense of the other), or amensalistic (one organism is inhibited or obliterated, while the other is unaffected). For example, most host–pathogen interactions are parasitic with the pathogen causing damage to the host. However, as mentioned above, periods of latency during an infection may be classed as a commensal relationship as damage to the host is minimal during this period. Interactions between members of the microbiome may be described as amensalistic as the presence of some species prevent the growth of others through nutrient depletion and the secretion of chemical mediators. This is an important factor as dysbiosis of the microbiome has been identified

Figure 1



Transition of *C. albicans* from commensal to parasite. During commensal growth *C. albicans* grows predominately as yeast and is tolerated by the host, and does not activate innate immune responses. Periods of dysbiosis and immune suppression permit *C. albicans* to proliferate, induce hyphal formation, and activate innate immune responses. At the vaginal mucosal, epithelial cells become sensitised resulting in hyperactivation of innate immune responses and neutrophil influx. This non-protective hyperactivation of neutrophils results in damage to the vaginal mucosa and symptomatic vaginal candidiasis.

as a major contributor for several fungal infections (i.e. vulvovaginal candidiasis, atopic dermatitis). Although common for bacterial species, the idea of mutualistic relationships between fungi and the human host is a new concept as the potential benefit to the host of harbouring fungi is still unknown (Figure 1).

Niche-specific fungal symbionts

Fungal symbionts vary in route of acquisition, niche/s inhabited, and ultimately, the type of symbiotic relationship formed. Some species are acquired at birth by direct transmission, leading to colonization of the skin and mucosal surfaces, while many fungal pathogens are ubiquitous within the environment, leading to constant exposure by oral or respiratory routes, as well as skin contact. Most of these exposures are transient, due to clearance by host immune responses or out competition for resources by the microbiome. However, changes in immune status or dysbiosis could lead to chronic colonisation and eventual host damage.

Mycobiome studies have been performed for most mucosal surfaces including the oral cavity [6], GI tract [7,8],

vagina [9,10], lung [11,12], and skin [13,14]. Over 75 genera of fungi have been identified in the oral cavity alone, which can seed the respiratory or GI tract mycobiome. The most common fungal species associated with the GI tract are *Candida*, *Saccharomyces* and *Cladosporium*, although DNA from more than 50 genera of fungi has been detected. Stability and fluctuations in population dynamics of the GI mycobiome is highly dependent on diet and host immune status. For example, *Saccharomyces cerevisiae* is commonly acquired from dietary sources and is considered to be a harmless or transient commensal. However, inflammatory bowel diseases [15] and some autoimmune diseases [16,17] are associated with increased levels of circulating *S. cerevisiae* antibodies (ASCA), which recognise fungal cell wall components [18]. Although it has been documented that *C. albicans* is an immunogen for development of ASCA [19], dietary *S. cerevisiae* can exacerbate symptoms in ASCA positive IBD patients [20]. In this situation, *S. cerevisiae* may be considered a parasitic symbiont. On the other end of the spectrum, a related species, *S. boulardii*, is used clinically as a probiotic treatment for gastroenteritis, acting as a mutualistic symbiont [21].

The vaginal mucosa is colonised by a variety of fungi and bacteria. Although *Candida* spp. are thought to be the predominate fungal colonisers of the vaginal mucosa, more recent microbiome studies have detected up to 20 genera of fungi in the vaginal niche, including *Candida*, *Aspergillus* and *Cladosporium* [22]. In healthy women, these fungal colonisers likely behave as commensal symbionts. However, many host and environmental factors including pregnancy, antibiotic usage and uncontrolled diabetes influence the vaginal microbiota and can result in dysbiosis and infection.

The dominant fungal commensal of the skin is *Malassezia* spp. [23], a lipophilic genus that consists mostly of plant pathogens. The lipid composition of the skin plays a role in controlling fungal colonisation, with *Malassezia globosa* being the predominate coloniser of the scalp and forehead and *Malassezia restricta* colonising the back [24]. However, *Malassezia* colonisation levels also correlate with a variety of skin diseases including psoriasis, dandruff, atopic dermatitis/eczema, seborrheic dermatitis, and pityriasis versicolor [25]. This suggests that above a certain threshold, these commensals act as parasitic symbionts, possibly due to increases in antigenic load. As evidence of this, it was shown that *M. sympodialis* secretes allergen-loaded exosomes that induce pro-inflammatory responses [26].

***Candida albicans*: the ubiquitous fungal symbiont**

C. albicans is a commensal fungus of the oral, gastrointestinal and genital tracts in up to 80% of healthy individuals. Under specific host and environmental conditions, *C. albicans* can transition from its commensal state to a parasitic state causing mucosal (oral and vaginal candidiasis) and life-threatening systemic disease. The polymorphic nature of *C. albicans* is a key virulence factor playing essential roles in the transition from commensalism to parasitism [27]. Several yeast-like morphologies aid *C. albicans* commensalism. For example, gastrointestinally induced transition (GUT) cells promote commensalism of *C. albicans* within the GI tract [28], grey cells enable colonisation of the tongue [29] and opaque cells have increased fitness on skin [30]. This repertoire of cell morphologies demonstrates the plasticity of *C. albicans* and its evolution as a human commensal.

Transition to damage-causing pathogen and disease

Commensalism of *C. albicans* on mucosal surfaces is thought to occur with yeast cells. In agreement with this, epithelial cells do not readily recognise the yeast form of *C. albicans* [31]. However, under periods of immune suppression, trauma and dysbiosis, abiotic and biotic cues induce *C. albicans* morphogenesis resulting in epithelial activation and induction of a proinflammatory response [31]. In vulvovaginal candidiasis (VVC), the vaginal epithelium becomes sensitised to *C. albicans*, and its activation results in significant neutrophil recruitment [2]. This

hyperactivation of the innate immune system generates a strong non-protective immune response that drives the immunopathology associated with VVC [2]. One question that arises is why do healthy women maintain *C. albicans* in a commensal relationship and what is the selective pressure that promotes persistent colonisation in the vagina? An answer to this question may lie in the location of the vagina between the rectum and urethra. The antagonistic relationships *C. albicans* exerts on many bacterial species, including those that cause potentially life threatening urinary tract infections, (UTIs), might inhibit migration of these pathogens from the rectum to the urethra, providing a selective pressure to maintain *C. albicans* in the vagina as a mutualistic symbiont. The primary etiological agent responsible for UTIs is uropathogenic *Escherichia coli* (>80% cases) [32]. *Candida* colonization of the vagina increases in puberty, coinciding with hormonal changes that promote fungal adherence and growth [33]. Prepubescent girls also have the highest occurrence of Gram-negative bacteria in the vagina (mainly *E. coli*), while the highest occurrence of *Candida* species is in women of child-bearing age [34]. This suggests that *Candida* inhibits *E. coli* in the vaginal environment either directly, or via colonization resistance, providing a microbiological barrier between the anus and urethra.

Asymptomatic oral carriage of *Candida* in the oral cavity is mediated via non-specific host barriers (saliva, antimicrobial peptides, among others) and strong immune defences. However, the onset of AIDS or use of cancer chemotherapy results in oropharyngeal candidiasis (OPC). The role of host factors in the predisposition to OPC is discussed below.

Entry of *C. albicans* into the bloodstream, via implanted medical devices, translocation from the gut during abdominal surgery or neutropenia, results in systemic infection. Key target organs include the kidney, spleen and liver, where *C. albicans* exerts excessive damage. Device associated infections permit the formation of drug and host resistant biofilms, which continually seed infections if not removed. Due to the lack of appropriate diagnostics and non-specific symptoms, infections are often misdiagnosed resulting in increased mortality rates.

Candidiasis and dysbiosis

Shifts in fungal populations leading to dysbiosis are associated with various diseases [35,36]. In this situation, members of the mycobiome transition from commensal to parasitic symbionts. Whether these shifts are causative or indicative of disease is likely a sliding scale as host and symbionts influence each other within the eco-system. Prolonged administration of antibiotic therapy predisposes women to VVC, suggesting that dysbiosis of the vaginal flora is a prerequisite for symptomatic *Candida* colonisation. Initially it was suggested that antibiotic treatment removed lactobacilli from the vaginal mucosa,

increasing vaginal pH, and promoting *Candida* hyphal formation. In agreement with this, lactobacilli have been proposed to reduce *Candida* colonisation [37^{*}], and have been explored as a potential probiotics [38]. However, other studies suggest that vaginal pH, and the lactobacilli population are not significantly altered in VVC [39], and that *Candida* colonisation is more common in women with a lactobacillus dominated microflora [40]. Therefore, the role of this amensalistic relationship warrants further investigation.

Treatment with oral antifungals perturbs the intestinal mycobiome, reducing the populations of *Candida*, whilst promoting the expansion of *Aspergillus*, *Wallemia* and *Epicoccum*, and causing increased allergic airway disease [41^{*}]. On the other hand, the use of oral antibiotics, depleted the bacterial composition of the GI microbiome, promoting the expansion of *Candida* [42]. The consequence of *Candida* overgrowth in the GI tract is still controversial. However, individuals with high *Candida* burdens appear to be more prone to intestinal inflammatory diseases [43], although the role of *Candida* remains to be determined.

Role of the host: genetic mutations

Genetic susceptibility to *C. albicans* infections varies according to site of infection, and not all infections are associated with genetic mutation. Systemic infection is associated with defects in innate immunity (neutrophil function) while oropharyngeal candidiasis (OPC) is associated with defects in cellular immunity (primarily CD4+ T cells). A major focus of recent genetic linkage studies is chronic mucocutaneous candidiasis (CMC), which is an infectious phenotype in patients with inherited or acquired T cell deficiency (primarily IL-17 immunity). CMC is an extremely rare familial disorder, with a current worldwide cohort <300 patients, and is characterized by chronic infection of skin, nails, and oral/genital mucosa [44^{**}]. Defects in *STAT1* result in CMC due to defects in IL-17, IFN- γ and IL-22 signalling [45]. IL-17 signalling is essential for controlling oral carriage of *Candida*, with defects in many of the signalling components resulting in OPC [46]. OPC can also result from an autoimmune disease where the patient generates antibodies to IL-17A, IL-17F and IL-22 [47].

Genetic predisposition to VVC is still an emerging topic. One study found higher frequencies in mutations associated with increased expression of mediators involved in mucosal tolerance (IL-22 and IDO1) in controls versus RVVC patients [48]. This study also found higher frequencies of a mutation causing a premature stop codon in the C-type lectin receptor Dectin-1 in women with RVVC, which mediates IL-22 production [48]. Polymorphisms in mannose binding lectin (MBL), a component of innate immunity that triggers complement activation, are also found at higher frequencies in RVVC patients and are

associated with leading reduced vaginal MBL levels [49,50]. Overall, these studies support the concept that pathways important in mucosal tolerance that may limit innate responsiveness to a commensal symbiont, promote resistance to RVVC.

Fungal factors

The most studied and important virulence attribute of *C. albicans* is its ability to reversibly switch morphologies, between yeast, pseudohyphal and true hyphal growth. Temperature, CO₂, pH, serum, quorum sensing molecules, nutrient availability and hypoxia all regulate morphogenesis [51]. As outlined above, each of these morphologies play distinct roles in colonisation and parasitism, and inhibition of morphogenesis dramatically inhibits fungal virulence. Other important virulence factors include the expression of adhesins (i.e. *ALS* family) and cell wall proteins (i.e. Hwp1) that enable attachment to host cells [52]. The Als5 adhesin is expressed during commensal growth, but repressed during pathogenicity. In agreement with Als5 playing a role in fungal commensalism, expression of *C. albicans* Als5 in *S. cerevisiae* promotes colonisation of the nematode gastrointestinal tract, without affecting survival [53]. Therefore, Als5 may be a critical factor for *C. albicans* commensalism. Once attached, *C. albicans* can actively penetrate mucosal barriers. The expression of SAPs is thought to be essential to this process, degrading proteins on host cells, and disrupting the host's protective barriers (i.e. degradation of mucin) [54]. Due to the role of SAPs in epithelial damage SAP expression is correlated with virulence rather than commensalism [29]. Finally, *C. albicans* induces epithelial damage through the secretion of candidalysin, a novel pore forming peptide. Candidalysin is predominately expressed by hyphal cells and is responsible for the majority of host damage exerted by *C. albicans* [55^{**}]. The role of candidalysin in commensalism has not been extensively studied, but deletion of candidalysin does reduce colonisation levels in murine models of OPC [55^{**}] suggesting that candidalysin may play roles in commensalism as well as pathogenesis. In addition to this repertoire of fungal virulence factors, *C. albicans* can also modulate the structure of its cell wall to either conceal or reveal immune stimulatory PAMPs on its surface [56^{*},57^{*},58^{*}]. This pliability of the cell wall architecture enables *C. albicans* to control the innate immune response. Therefore, *C. albicans* has uniquely positioned itself as a commensal symbiont, with a plethora of ways to sense and respond to changes within the host that ensure successful transition from commensalism to parasitism and initiation of disease during periods of weakened host defences.

Conclusion

Fungi form an important part of our microbiome, with symbiotic relationships ranging from commensal to parasitic. The symbiotic relationship between humans and

fungi is greatly underappreciated and under researched. Given that many fungi are opportunistic pathogens, understanding the balance and transitions between these relationships is vital for the future of medical mycology.

Conflict of interest

Nothing declared.

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