

**ADVANCED REVIEW**

# The mammalian mycobiome: A complex system in a dynamic relationship with the host

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Mammalian barrier surfaces are densely populated by symbiont fungi in much the same way the former are colonized by symbiont bacteria. The fungal microbiota, otherwise known as the mycobiota, is increasingly recognized as a critical player in the maintenance of health and homeostasis of the host. Here we discuss the impact of the mycobiota on host physiology and disease, the factors influencing mycobiota composition, and the current technologies used for identifying symbiont fungal species. Understanding the tripartite interactions among the host, mycobiota, and other members of the microbiota, will help to guide the development of novel prevention and therapeutic strategies for a variety of human diseases.

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host-microbe interactions, immunology, microbiome, mycobiome, mycobiota

## 1 | INTRODUCTION

The human body carries vast and diverse communities of symbiotic microbes that are important for human health and development. Conversely, alterations in the microbiota from the normal state, or microbial dysbiosis, is often implicated in the pathogenesis of diseases, such as inflammatory bowel disease (IBD), metabolic disorders, allergies, and disorders of the central nervous system. Over the past decade, most of the research efforts on the microbiome have focused on characterizing bacteria in healthy and diseased states while neglecting fungi, because of the relatively low abundance of the latter and various technical challenges ranging from sample preparation to inadequate reference databases. In fact, diverse symbiont fungi have been isolated from the skin, mouth, gut, respiratory tract, and other mucosal surfaces. A summary of our current knowledge of the predominant members of the fungal microbiota—also known as the mycobiota—which colonizes various barrier surfaces in humans, is provided in Table 1. While bacteria vastly outnumber fungi across most host sites, fungi are significantly larger than bacteria in cell size and possess specialized metabolic gene clusters in response to specific ecological needs (Wisecaver, Slot, & Rokas, 2014). The most frequently reported human-associated fungal species belong to the following genera: *Candida*, *Saccharomyces*, *Malessezia*, *Aspergillus*, *Fusarium*, and *Cladosporium*. For discussion of these fungi and their effects on host physiology, we direct the reader to other reviews (Limon, Skalski, & Underhill, 2017).

Despite its underrepresentation in the microbiome and in the literature, the mycobiota can exert dramatic health effects, from the beneficial roles played by symbiotic fungi on host immunity to the deleterious effects of the same fungi under dysbiotic conditions. In both cases, the health outcomes are often determined by the way microbes interact among themselves and

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TABLE 1 Composition of fungi and bacteria at different anatomical sites in humans

Body site	Composition and relative abundance in healthy humans		References (for fungi)
	Predominant fungal genera	Predominant bacterial genera	
Mouth	<i>Candida</i> , <i>Aspergillus</i> , <i>Cladosporium</i> , <i>Saccharomyces</i> , <i>Fusarium</i> , <i>Penicillium</i> , <i>Pichia</i> , <i>Cryptococcus</i>	<i>Streptococcus</i> , <i>Prevotella</i> , <i>Veillonella</i> , <i>Haemophilus</i> , <i>Fusobacterium</i> , <i>Neisseria</i> , <i>Corynebacterium</i>	Ghannoum et al. (2010)
Gastrointestinal tract (intestinal/stool)	<i>Candida</i> , <i>Saccharomyces</i> , <i>Fusarium</i> , <i>Debaromyces</i> , <i>Penicillium</i> , <i>Galactomyces</i> , <i>Pichia</i> , <i>Cladosporium</i> , <i>Malassezia</i> , <i>Cyberlindnera</i> , <i>Aspergillus</i>	<i>Bacteroides</i> , <i>Clostridium</i> , <i>Prevotella</i> , <i>Alistipes</i> , <i>Lactobacillus</i> , <i>Eubacterium</i> , <i>Ruminococcus</i> , <i>Bifidobacterium</i>	Hoffmann et al. (2013), Nash et al. (2017), Strati, Di Paola, et al. (2016)
Skin	<i>Malassezia</i> , <i>Aspergillus</i> , <i>Candida</i>	<i>Staphylococcus</i> , <i>Corynebacterium</i> , <i>Propionibacterium</i> , <i>Micrococcus</i>	Oh et al. (2013)
Lower respiratory tract	<i>Aspergillus</i> , <i>Candida</i> , <i>Clavispora</i>	<i>Prevotella</i> , <i>Veillonella</i> , <i>Streptococcus</i>	van Woerden et al. (2013)
Genitourinary tract (vagina)	<i>Candida</i> , <i>Cladosporium</i> , <i>Pichia</i> , <i>Aspergillus</i> , <i>Rhodotorula</i>	<i>Lactobacillus</i> , <i>Gardnerella</i>	Drell et al. (2013)

with the human host, rather than via simple host–microbe relationships. Notwithstanding the clear importance of these interactions, our ability to manipulate them to improve health is often rudimentary at best, given that it is incredibly difficult to untangle the myriad complex and dynamic interactions that occur within a heterogeneous microbial community in a host environment. In this review, we will discuss the effects of the mycobiota on the host during homeostatic and diseased states, factors that influence the diversity of the mycobiota, methods and challenges in current mycobiota study and characterization, and how we can improve upon existing research efforts in the mycobiome field.

## 2 | WHY DOES THE MYCOBIOME MATTER?

### 2.1 | Mycobiota in health

Whereas the impact of the bacterial microbiota on host physiology is relatively well described, much less is known about the interactions between the mycobiota and the host and the ensuing effects on the host. Foster et al. have argued that hosts are under strong selective pressure to control and mold their microbiota towards the retention of beneficial species (Foster, Schluter, Coyte, & Rakoff-Nahoum, 2017). By this reasoning, one would predict that the mycobiota has also undergone selection by the host to provide advantages to the latter. Accordingly, a limited number of studies—to be detailed in the following sections—have demonstrated a role for symbiont fungi in mediating tissue homeostasis.

#### 2.1.1 | Symbiont fungi calibrate host immunological responses

The ability of symbiont bacteria and viruses to calibrate the baseline immunological responsiveness of the host is well-delineated, and we refer the reader to several excellent reviews for more information on the specific mechanisms involved (Cho & Blaser, 2012; Chung & Kasper, 2010; Jarchum & Pamer, 2011; Virgin, 2014). Furthermore, recent work by the Human Functional Genome Project (Netea et al., 2016) has identified associations between certain symbiont bacterial species and anti-microbial cytokine responses of peripheral blood mononuclear cells (PBMCs) in healthy people, in support of a role for the microbiota in modifying systemic immune responses in humans (Schirmer et al., 2016).

Evidence for an analogous immunomodulatory role for symbiont fungi (discussed in Hall & Noverr (2017), Rizzetto, De Filippo, & Cavalieri (2014)) has been limited largely to in vitro studies (Rizzetto et al., 2010, 2016) and in vivo infection or disease models in rodents (Iliev et al., 2012; Murdock et al., 2011; Wheeler et al., 2016). However, a recent study by Jiang et al. (2017) indicates that the mycobiota in and of itself can indeed substitute for symbiont bacteria and viruses in modulating homeostatic immunological functions both systemically and in mucosal tissue in mice. Antibiotics-treated mice developed more fulminant dextran sodium sulfate (DSS)-induced colitis and generated reduced levels of protective CD8<sup>+</sup> T cells when infected with influenza A virus; oral inoculation of antibiotics-treated mice with two common members of the gut mycobiota, *Saccharomyces cerevisiae* and *Candida albicans*, sufficed to mitigate both aforementioned defects (Jiang et al., 2017). The protective impact of the two fungal species could be recapitulated by the inoculation of mannans, an abundant component of fungal cell walls. The pathways underlying these broad effects of symbiont microbes on host physiology remain ambiguous, though several possibilities exist, some of which are discussed in the following sections. For instance, the phenotype and differentiation of the monocyte-macrophage compartment is strongly influenced by the intestinal microbiota in mice (Chang, Hao, Offermanns, & Medzhitov, 2014; Ganai et al., 2012; Khosravi et al., 2014; Trompette et al., 2018), and human monocytes stimulated in vitro with chitin or  $\beta$ -glucan, which represent other fungal cell wall determinants, evince sustained changes in their potential for secreting pro-inflammatory cytokines (Quintin et al., 2012; Rizzetto et al., 2016). There, however, exists

considerable variation in the capacity of fungi (and fungal cell wall components) to modulate immunocyte activity at the strain and species level (Rizzetto et al., 2010, 2013, 2016; Wagener, MacCallum, Brown, & Gow, 2017). It is therefore likely that diverse symbiotic fungal species can tune homeostatic immune responses via differential host sensing of fungal determinants such as mannans, with the net effect dependent on the composition of the mycobiota in each individual (Rizzetto et al., 2014).

### 2.1.2 | Symbiont fungi promote development of peripheral lymphoid organs

Germ-free mice present with underdeveloped secondary lymphoid organs (SLOs), including a reduced volume and cellularity in both gut-proximal and gut-distal lymph nodes. This defect in the formation of lymphoid structures impairs the ability of the host to mount protective adaptive immune responses to infections (van de Pavert et al., 2014). Interestingly, Shi and coworkers identified symbiont fungi but not bacteria as primary drivers of the maturation of SLOs in mice (Z. Zhang et al., 2016). Development of SLOs requires a wave of migration of dendritic cells (DCs) expressing the retinol dehydrogenase enzyme, RALDH, from the intestines into peripheral lymph nodes in neonatal mice. The arrival of these RALDH<sup>+</sup> DCs promotes a switch in the local expression of adhesion molecules from MAdCAM-1 to PNAd, which in turn binds L-selectin on naïve T cells and mediates their recruitment into and recirculation throughout the SLO network in the body. Treatment of mice with antifungals but not antibiotics diminishes the migration of RALDH<sup>+</sup> DCs into SLOs, while inoculation of neonates with a single species of the murine indigenous mycobiota, *Candida tropicalis*, augmented the numbers of RALDH<sup>+</sup> DCs in lymph nodes. However, the mechanisms by which symbiotic fungi promote the trafficking of RALDH<sup>+</sup> DCs into SLOs remain unknown, nor is it apparent if the effect of *C. tropicalis* on SLO development is common to other members of the mycobiota.

### 2.1.3 | Symbiont fungi promote T cell responses

Mucosal and systemic fungal infections typically provoke CD4<sup>+</sup> T cell (Th17 and Th1) responses characterized by the production of the cytokines interleukin (IL)-17A and interferon (IFN)- $\gamma$ , respectively (Kashem et al., 2015). An assortment of evidence supports a role for the mycobiota in promoting similar T cell responses at steady-state. Germ-free or antibiotics-treated mice colonized with *C. albicans* developed robust colonic Th17 responses without any overt signs of intestinal inflammation (Atarashi et al., 2015; Leonardi et al., 2018), and antibiotics-treated mice gavaged with *C. albicans* generated memory and effector T cells in the gut (Xin et al., 2014). In healthy people, memory T cells specific for *C. albicans* and *Aspergillus fumigatus* can be isolated from the peripheral blood (Bacher et al., 2014). Circulating *A. fumigatus*-specific T cells are primarily Th1 cells (Chaudhary, Staab, & Marr, 2010; Hebart et al., 2002; Jolink et al., 2013), although the predominant T cell subset induced by the fungus likely varies considerably among individuals due to substantial intra-strain variation in inducing Th1 versus Th17 populations (Rizzetto et al., 2013). On the other hand, *C. albicans*-specific T cells in human blood typically secrete the cytokines IL-17A, IL-22, and IFN- $\gamma$  but not IL-10, thereby presenting a mixed Th1-Th17 phenotype (Zielinski et al., 2012). Healthy individuals also harbor a circulating subset of Th9 cells that secrete the cytokine IL-9, and the majority of Th9 cells are specific for *C. albicans* and express the skin-homing receptor, cutaneous leucocyte-associated antigen (CLA) (Schlapbach et al., 2014). In contrast, *C. albicans*-specific Th17 cells typically express the gut-homing integrin  $\alpha_4\beta_7$  (Schlapbach et al., 2014). Thus, *C. albicans* (and by extension, other symbiotic fungi) can drive diverse and functional T cell responses in a tissue-contextual fashion. Since microbiota-induced T cell subsets have been described to mediate heterologous protection against other pathogens at the mucosal surface (Ivanov et al., 2009; Naik et al., 2015), we hypothesize that mycobiota-driven T cell subsets and other immunocyte populations can similarly confer the host with cross-protection against other infections.

*A. fumigatus* and *C. albicans* are pathobionts—symbionts that are ordinarily benign but that can turn pathogenic under certain circumstances—and it remains possible that the Th1 and Th17 populations elicited by the two fungal species represents a pro-inflammatory response to subclinical infections rather than a homeostatic response. Interestingly, *S. cerevisiae*, another common member of the mycobiota that neither forms hyphae nor causes infections in people, can also induce both Th1 and Th17 subsets from human CD4<sup>+</sup> T cells in vitro (Rizzetto et al., 2010). *S. cerevisiae* yeasts promote Th1 differentiation while the sporulated form favors Th17 induction. The divergent effects of *S. cerevisiae* yeasts and spores and *C. albicans* on T cell responses were traced to a differential impact of fungal mannans on DCs that in turn prime the T cells (Rizzetto et al., 2010, 2012). Hence both nonpathogenic and pathobiont members of the mycobiota can drive robust T cell responses via a diversity of mechanisms.

Since the host immune system has to remain tolerant towards the mycobiota to maintain homeostasis, the inflammatory T cell subsets generated in response to symbiotic fungi are likely countervailed by regulatory immunocyte populations. Indeed, Foxp3<sup>+</sup> regulatory T (Treg) cells specific to *C. albicans* and *A. fumigatus* have been detected in the peripheral blood of healthy individuals, whereby they outnumber their fungus-specific effector T cell counterparts (Bacher et al., 2014). Whether fungus-specific Treg cells are capable of dampening excessive inflammation in the context of nonfungal infections such as autoimmunity and bacterial infections remains unclear, though this possibility is implied by the precedent of bacteria-specific Treg populations mitigating the severity of colitis and allergic diarrhea in mice (Atarashi et al., 2011, 2013).

### 2.1.4 | Fungi train host immunity

Recent studies have demonstrated that two common members of the intestinal mycobiota, *C. albicans* and *S. cerevisiae*, are capable of eliciting a form of innate immunological memory in myeloid cells, a phenomenon known as trained immunity (Netea, Quintin, & van der Meer, 2011). Trained immunity refers to the heightened immune response to a secondary infection that, unlike classical immunological memory, occurs independently of the adaptive immune system and can be directed against both the causative microbe of the primary infection and other microbes (Netea et al., 2011). Human monocytes pre-exposed to *C. albicans* or *S. cerevisiae* produced elevated amounts of pro-inflammatory cytokines, including IL-6 and TNF- $\alpha$ , upon subsequent stimulation with various infectious stimuli such as toll-like receptor ligands (Quintin et al., 2012; Rizzetto et al., 2016). The authors then identified  $\beta$ -1,3-glucan and chitin as sufficient to recapitulate the training effects of *C. albicans* and *S. cerevisiae* on myeloid cells, respectively. Accordingly, mice treated with  $\beta$ -1,3-glucan or chitin were significantly protected from a subsequent systemic challenge with *C. albicans* compared to untreated controls (Quintin et al., 2012; Rizzetto et al., 2016). It is tempting to speculate that resident *C. albicans* and *S. cerevisiae* cells can train mucosal or circulating myeloid cells via similar mechanisms, thereby raising the baseline resistance of the host to other pathogens. An analogous effect has already been described for intestinal symbiotic bacteria, which enhance the antimicrobial activity of neutrophils systemically via shedding of peptidoglycan, a component of bacterial cell walls (Clarke et al., 2010). Mechanistically, trained immunity in myeloid cells by fungal  $\beta$ -glucan requires substantial rewiring of cellular metabolism, including an increase in aerobic glycolysis and adaptations in cholesterol biosynthesis, which in turn promote epigenetic remodeling of genes involved in inflammation (Arts et al., 2016; Bekkering et al., 2018; Cheng et al., 2014; Mitroulis et al., 2018). Of note, *S. cerevisiae* strains exhibiting the highest chitin content and the strongest capacity for training monocytes were clinical isolates from human stools and not laboratory or environmental isolates (Rizzetto et al., 2016), suggesting host selection of fungal strains for their immunostimulatory properties.

### 2.1.5 | Fungal metabolites and potential impact on host immunity

Fungal symbionts, like their bacterial counterparts, secrete or promote the host-mediated generation of a variety of metabolites that can potentially modulate host tissue function. A recent study found that *S. cerevisiae*, a common component of the intestinal mycobiota, exacerbated the progression of DSS-induced colitis in mice by enhancing host purine metabolism and thereby increasing the systemic levels of uric acid (Chiaro et al., 2017). On cutaneous surfaces, members of the dominant fungal genus *Malassezia* produce metabolites such as malassezin, pityriacitrin, and indolo[3,2-*b*]carbazole that serve as potent ligands for the aryl hydrocarbon receptor (Ahr) (Gaitanis et al., 2008; Magiatis et al., 2013; Mexia et al., 2015). Ahr is expressed at high levels by many cells in the skin where it promotes epithelial repair, melanogenesis, and barrier homeostasis (Esser & Rannug, 2015; Furue, Takahara, Nakahara, & Uchi, 2014). Moreover, Ahr signaling is crucial for the development and function of panoply of immunocytes, including cutaneous invariant  $\gamma\delta$  T cells, IL-22-producing type 3 innate lymphoid cells, Treg cells, Th17 cells, and DCs (Cella & Colonna, 2015; Quintana & Sherr, 2013; Vlachos, Schulte, Magiatis, Adema, & Gaitanis, 2012). *Malassezia* species also secrete lipases and phospholipases to convert host triglycerides abundant on the skin into short-chain fatty acids (SCFAs), which serve as metabolic substrates for the fungi (Velegraki, Cafarchia, Gaitanis, Iatta, & Boekhout, 2015; White et al., 2014). However, these SCFAs can manifest antimicrobial and immunomodulatory activities, as evidenced by the ability of one such metabolite, azelaic acid, to inhibit bacterial and fungal growth in vitro and to dampen the inflammatory response of human keratinocytes to ultraviolet irradiation (Brasch & Christophers, 1993; Mastrofrancesco et al., 2010; Schulte, Wu, & Rosen, 2015). SCFAs and other metabolites derived from symbiotic bacteria in the gut have been described to exert wide-ranging immunomodulatory effects in vivo (Shapiro, Thaiss, Levy, & Elinav, 2014). We postulate that metabolites derived from the mycobiota, many of which remain undefined, could similarly influence host tissue function.

## 2.2 | Mycobiota in disease

Dysbiosis of the bacterial microbiota has been associated with, and in a few cases shown to be causative of, a variety of pathologies both in humans and in several model organisms. The growing recognition of the contributions of the mycobiota to host immunity and health has also led to a burgeoning number of studies on the role of the mycobiota in human disease (Table 2).

### 2.2.1 | Inflammatory bowel disease

Changes in the mycobiome, like those described for the bacterial microbiome, have been associated with the penetrance and expressivity of IBD in people (Iliev & Leonardi, 2017; Limon et al., 2017; Table 2). In particular, an overgrowth of *C. albicans* and related *Candida* species is often observed in mice and humans afflicted with IBD (Chehoud et al., 2015; Hoarau et al., 2016; Lewis et al., 2015; Li et al., 2014; Liguori et al., 2016; Ott et al., 2008; Qiu et al., 2015, 2017; Sokol et al., 2017). On the other hand, *S. cerevisiae* was found to decline in abundance in IBD patients and during active flare (Liguori et al., 2016;

TABLE 2 Mycobiota and disease

Disease	Mycobiota alterations in diseased individuals	Organism	References
Inflammatory bowel disease: Crohn's disease (CD) and ulcerative colitis (UC)	Increased fungal diversity	Human	Li et al. (2014), Ott et al. (2008)
	No change in fungal diversity (UC)	Human	Qiu et al. (2017)
	Reduced fungal diversity	Human	Chehoud et al. (2015), Liguori et al. (2016)
	Increased levels of <i>Candida</i> , <i>Gibberella moniliformis</i> , <i>Alternaria brassicicola</i> , and <i>Cryptococcus neoformans</i> in mucosa of CD patients	Human	Li et al. (2014)
	Increased levels of <i>Candida</i> and reduced levels of <i>Cladosporium</i>	Human	Chehoud et al. (2015)
	Increased levels of <i>Candida albicans</i> , <i>Saccharomyces cerevisiae</i> , <i>Clavispora lusitanae</i> , <i>Cyberlindnera jadinii</i> , and <i>Kluyveromyces marxianus</i> in pediatric CD	Human	Lewis et al. (2015)
	Increased levels of <i>Candida tropicalis</i> in familial CD	Human	Hoarau et al. (2016)
	Increased levels of <i>C. albicans</i> and reduced levels of <i>S. cerevisiae</i>	Human	Sokol et al. (2017)
	Increased levels of <i>Candida glabrata</i> , <i>Dioszegia</i> , and Cystofilobasidiaceae family in inflamed mucosa and increased levels of <i>S. cerevisiae</i> and <i>Filobasidium uniguttulatum</i> in healthy mucosa of CD subjects	Human	Liguori et al. (2016)
	Increased levels of <i>Candida</i> , <i>Wickerhamomyces</i> , and especially <i>Aspergillus</i> in the mucosa of UC patients	Human	Qiu et al. (2017)
	Outgrowth of <i>C. tropicalis</i> and <i>Trichosporon</i> and reduced <i>S. cerevisiae</i>	Mouse	Iliev et al. (2012)
	Increased levels of <i>Penicillium</i> , <i>Wickerhamomyces</i> , <i>Alternaria</i> , and <i>Candida</i> species, and reduced levels of <i>Cryptococcus</i> , <i>Phialemonium</i> , and <i>Wallemia</i> in colitic mice; mucosal levels of fungi increased while luminal levels unchanged	Mouse	Qiu et al. (2015)
	Increased levels of <i>Aspergillus amstelodami</i> , <i>Epicoccum nigrum</i> , <i>Wallemia sebi</i> and reduced levels of <i>Penicillium brevicompactum</i> and <i>C. tropicalis</i> in mice predisposed to colitis	Mouse	Wheeler et al. (2016)
<i>C. albicans</i> inoculation exacerbates induced colitis in rats	Rat	Zwolinska-Wcislo et al. (2009)	
Allergic airway disease	Elevated levels of <i>Candida</i> and <i>Rhodotorula</i> species in stools	Human neonates	Fujimura et al. (2016)
	Outgrowth of <i>C. tropicalis</i> in intestines upon antibiotics treatment	Mouse	Y. G. Kim et al. (2014)
	Outgrowth of <i>A. amstelodami</i> , <i>E. nigrum</i> , <i>W. sebi</i> , and reduced levels of <i>P. brevicompactum</i> and <i>C. tropicalis</i> upon prolonged antifungal treatment	Mouse	Wheeler et al. (2016)
Chronic obstructive pulmonary disease (COPD)	Increased frequency of <i>Pneumocystis jirovecii</i> colonization in patients with COPD versus those with non-COPD lung diseases, and <i>Pneumocystis</i> colonization is associated with severity of airflow obstruction	Human	Calderon et al. (2007), George, Kannass, Huang, Sciuuba, and Morris (2009), Morris et al. (2004)
	<i>Pneumocystis</i> colonization aggravates COPD in monkeys colonized with simian/human immunodeficiency virus	Nonhuman primate	Shiple et al. (2010)
	<i>Pneumocystis</i> colonization combined with exposure to cigarette smoke exacerbates pulmonary inflammation and destruction characteristic of COPD	Mouse	Christensen et al. (2008)
Pityriasis versicolor	Infection of skin by <i>Malassezia</i> spp., in particular <i>M. globosa</i>	Human	Harada, Saito, Sugita, and Tsuboi (2015), Velegraki et al. (2015), White et al. (2014)
Malassezia folliculitis	Invasion of hair follicles by <i>Malassezia</i> spp., in particular <i>M. globosa</i>	Human	
Seborrheic dermatitis and atopic dermatitis	Controversial—Both positive and no associations with <i>Malassezia</i> species have been reported	Human	Reviewed in Prohic, Jovovic Sadikovic, Krupalija-Fazlic, and Kuskunovic-Vlahovljak (2016)
Alcoholic liver disease	Increased total fungal load and decreased fungal diversity; elevated levels of <i>Candida</i> species, in particular <i>C. albicans</i> and <i>C. dubliniensis</i> ; reduced levels of <i>Debaryomyces</i> , <i>Galactomyces</i> , and <i>Epicoccum</i>	Mouse, human	Yang et al. (2017)

(Continues)



TABLE 2 (Continued)

Disease	Mycobiota alterations in diseased individuals	Organism	References
Neurological disorders: Rett syndrome (RTT) and autism spectrum disorders (ASD)	Increased levels of <i>Candida parapsilosis</i> and reduced levels of <i>C. albicans</i> in RTT patients; <i>C. parapsilosis</i> isolates from stools of RTT patients are genetically distinct from and more virulent than those from healthy controls; increased <i>Candida</i> spp. in individuals with ASD	Human	Strati et al. (2016, 2017, 2018), Strati et al. (2016), Strati et al. (2017)
Metabolic syndrome	Reduced levels of <i>Mucor racemosus</i> and <i>M. fuscus</i>	Human	Mar Rodriguez et al. (2015)
	Reduced levels of <i>S. cerevisiae</i> , <i>Tilletiopsis washingtonensis</i> , <i>Alternaria</i> , <i>Septoriella</i>	Mouse	Heisel et al. (2017)

Sokol et al., 2017), a result that has been reproduced in mice (Iliev et al., 2012). Of note, fungal communities likely differ between the mucosa and the lumen, and along different sections of the intestines (Liguori et al., 2016; Qiu et al., 2015, 2017), and it remains a challenge to determine where the predictive or causative fungal symbionts in IBD reside.

While it is unclear from many of the preceding studies whether fungal dysbiosis contributes to or is merely an epiphenomenon of intestinal inflammation, some evidence exists in support of an increased antifungal inflammatory response and an etiological role for the mycobiota during IBD. Crohn's disease (CD) patients are well known to develop higher titers of anti-*S. cerevisiae* antibodies, which target mannan in fungal cell walls, suggesting an active immunological response towards symbiotic fungi that might contribute to disease. Moreover, oral inoculation of mice with *C. albicans* (Jawhara et al., 2008) or *C. tropicalis* (Iliev et al., 2012) provoked more fulminant DSS-induced colitis. In a separate study, monocolonization of germ-free mice with *S. cerevisiae* but not another fungal symbiont, *Rhodotorula aurantiaca*, aggravated colitis (Chiaro et al., 2017). Mutations in fungal sensing pathways that predispose towards IBD such as dectin-1 (encoded by *CLEC7A*), which detects  $\beta$ -glucan, and *CARD9*, which transduces signals from dectin-1, are also associated with fungal dysbiosis and a susceptibility to IBD. Indeed, patients carrying a particular *CLEC7A* haplotype were found to develop severe refractory ulcerative colitis (UC), a finding replicated in mice wherein *Clec7a*-deficient mice manifested fungal dysbiosis characterized by an overgrowth of *C. tropicalis* and suffered worse colonic inflammation (Iliev et al., 2012). Individuals harboring a nonsynonymous single nucleotide polymorphism (SNP) in *CARD9* bear a significantly elevated risk of developing IBD (Franke et al., 2010; McGovern et al., 2010), while those carrying a different splice-site variant of the same gene are protected from disease (Rivas et al., 2011). In addition, colitis in *Card9*-knockout (KO) mice is partially alleviated by antifungal drugs (Sokol et al., 2013). The collective evidence therefore points to a role for the gut mycobiota, interacting with the host genetic background and an array of other factors such as the diet and the environment, in shaping an individual's susceptibility to IBD.

### 2.2.2 | Allergic airway diseases

Many fungal species, in particular *Aspergillus* species, have been implicated in the development of allergic diseases such as allergic rhinitis and asthma, because fungal spores are often potent allergens (Rick, Woolnough, Pashley, & Wardlaw, 2016; I. Zhang, Pletcher, Goldberg, Barker, & Cope, 2017). Antibiotic use, which promotes the outgrowth of symbiotic fungi, is also associated with an increased risk for asthma and allergies (Huffnagle, 2010). Indeed, antibiotic treatment coupled with oral inoculation of *C. albicans* promoted the development of an allergic airway response to *A. fumigatus* in mice compared to nonantibiotics-treated controls (Noverr, Noggle, Toews, & Huffnagle, 2004). Another study observed an overgrowth of autochthonous intestinal *Candida* species after antibiotics treatment, which in turn predisposed the mice to allergic airway inflammation (Y. G. Kim et al., 2014). Mechanistically, fungus-derived prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) emanated from the gut to the periphery, where it promoted the development of type 2 immunological responses that mediate allergic disease. Since many fungal species secrete PGE<sub>2</sub> in vitro (Noverr, Toews, & Huffnagle, 2002), the PGE<sub>2</sub> signaling axis might represent a common pathway by which fungal symbionts promote the development of allergic disorders. Of note, Wheeler et al. (2016) found that sustained antifungal drug treatment, much like antibiotics administration, caused mice to generate heightened airway allergic responses to house dust mite extract. Antifungals altered the gut mycobiota composition and the introduction of three fungal species enriched by prolonged antifungal treatment—*Aspergillus amstelodami*, *Epicoecum nigrum*, and *Wallemia sebi*—into untreated mice was sufficient to accelerate the development of allergic disease (Wheeler et al., 2016). In support of a role for intestinal fungi in modulating the risk of allergic disease in humans, *Candida* and *Rhodotorula* species were found to be enriched in the fecal microbiotas of neonates who went on to develop multisensitized atopy and asthma (Fujimura et al., 2016). A recent study also identified an SNP in *CLEC7A* that is associated with reduced dectin-1 expression and diminished lung function in asthmatic subjects (Gour et al., 2018). While the authors linked the *CLEC7A* polymorphism to impaired immune responses to tropomyosin, a conserved invertebrate determinant, it seems plausible that anomalous sensing of symbiotic fungi and the ensuing alterations in the mycobiota might also be a contributing factor (Gour et al., 2018).

### 2.2.3 | Skin disease

*Malassezia* species provoke the skin diseases pityriasis versicolor (PV) and *Malassezia* folliculitis (MF) and have also been implicated in other inflammatory skin disorders, including seborrheic dermatitis (SD) and atopic dermatitis (AD) (Harada et al., 2015; Velegraki et al., 2015; White et al., 2014). PV is a chronic superficial infection of the skin by *Malassezia* characterized by hypo- or hyper-pigmented lesions, while MF results from the invasion of the hair follicles by *Malassezia* species. *M. globosa* represents the dominant fungal species in cultures from PV and MF lesions, though other species such as *M. restricta* and *M. sympodialis* have also been detected (Harada et al., 2015; White et al., 2014). On the other hand, evidence for the association of specific *Malassezia* strains or an increased burden of *Malassezia* with SD and AD remains contradictory (Prohic et al., 2016), likely due in part to the abundance of *Malassezia* species on healthy skin and poor resolution in discriminating between *Malassezia* species at the strain level. Nonetheless, treatment of SD and AD patients with antifungals reduces *Malassezia* load and alleviates disease symptoms in a subset of individuals, in support of a role for *Malassezia* in these ailments (Harada et al., 2015; White et al., 2014). In addition, AD patients display increased T cell reactivity, skin-prick-test positivity, and circulating levels of immunoglobulin E, to *Malassezia*, relative to healthy subjects (Harada et al., 2015; White et al., 2014), indicating an active antifungal immune response that might contribute to disease.

### 2.2.4 | Alcoholic liver disease

Apart from modulating gut-associated inflammation, intestinal fungal dysbiosis was also reported to exacerbate alcoholic liver disease (ALD) in mice and humans (Yang et al., 2017). The composition of the mycobiota in individuals with ALD became increasingly divergent from that of healthy people as disease progressed and became dominated by *Candida* species. Consistent with the findings in humans, ethanol-fed mice also exhibited fungal dysbiosis characterized by an overgrowth of *Candida* species. Moreover, fungal overgrowth aggravated liver inflammation and disease severity by increasing the translocation of  $\beta$ -glucans from the gut to the liver, where they activated the resident macrophages known as Kupffer cells via dectin-1 to secrete IL-1 $\beta$ . Accordingly, antifungal drug treatment corrected the fungal outgrowth, reduced IL-1 $\beta$  secretion by Kupffer cells, and ameliorated liver pathology and ALD severity. A different study by Bajaj et al. (2018) similarly identified fungal dysbiosis in the guts of cirrhotic patients. Alterations in the mycobiome was additionally linked to bacterial dysbiosis, and a combined bacterial–fungal dysbiosis metric—the ratio of Bacteroidetes to Ascomycota—independently predicted cirrhotic progression as defined by hospitalization after a 90-day follow-up.

### 2.2.5 | Autoimmunity

Evidence for a role of fungi in autoimmune diseases is scant, though a study on the SKG (also known as Zap70) mouse model of rheumatoid arthritis (RA) demonstrates that fungi can contribute to autoimmune inflammation. SKG mice suffer from a spontaneous onset of RA, and disease is attenuated upon delivery of antifungals (Yoshitomi et al., 2005). Conversely, injection of SKG mice with  $\beta$ -glucans amplifies disease severity. Th17 cells were subsequently identified as the cell type induced by fungi that provoked inflammation in the joints of arthritic mice (Hirota et al., 2007). Intriguingly, both dysbiosis of the microbiota and Th17 responses are associated with an array of inflammatory and autoimmune disorders, including RA, multiple sclerosis, IBD, and psoriasis (Gaffen, Jain, Garg, & Cua, 2014; Gevers et al., 2014; Scher et al., 2013). Since fungi typically trigger robust Th17 responses, it is plausible that changes in the mycobiota can similarly promote the development of autoimmunity in predisposed individuals via the induction of pathogenic Th17 cells.

### 2.2.6 | Neurological disorders

There is growing data in mice and humans that implicates the intestinal microbiota in a variety of neurological disorders (Collins, Surette, & Bercik, 2012; Fung, Olson, & Hsiao, 2017). For instance, transfer of the microbiota derived from Parkinson's disease patients into mice aggravated motor deficits in the recipients when compared with animals transplanted with microbiota from healthy donors (Sampson et al., 2016). Similar demonstrations of a causative role for the mycobiota in neurological disorders have yet been published, but several studies linking fungal dysbiosis to disease in people hint at a contribution from symbiotic fungi. *Candida* species are over-represented in the stools of individuals with autism spectrum disorders (Iovene et al., 2017; Strati et al., 2017) and Rett syndrome (RTT), a progressive neurological disorder (Strati, Cavalieri, et al., 2016), relative to those of healthy controls. Intriguingly, fecal *Candida parapsilosis* isolates from RTT patients are genetically distinct from those in healthy people and display traits of heightened virulence, such as an enhanced ability to form biofilms and to elicit the production of pro-inflammatory cytokines from human PBMCs in vitro, providing a potential link between intestinal fungi and the increased inflammatory tone in the gut and nervous system that is frequently observed in people afflicted with RTT and other neurological diseases (Strati et al., 2018).

### 2.2.7 | Metabolic syndrome

Metabolic syndrome is a collection of conditions associated with obesity in people and which predisposes them towards cardiovascular disease and type 2 diabetes. Dysbiosis of the intestinal bacterial microbiome is associated with metabolic syndrome (Sonnenburg & Backhed, 2016), and an etiological role for the microbiota in promoting obesity in mice has also been reported (Ridaura et al., 2013; Turnbaugh et al., 2006). Of note, alterations in the composition of the gut fungal community were also observed in obese mice and humans (Heisel et al., 2017; Mar Rodriguez et al., 2015), although a causative link has yet to be established. Given the ability of symbiotic fungi to interact with gut bacteria and influence host immunity, it is tempting to posit a role for the mycobiota in modulating host susceptibility to obesity and metabolic syndrome as well.

## 3 | WHAT INFLUENCES THE MYCOBIOME COMPOSITION?

The mycobiome composition in or on the human body varies across individuals and has been implicated in diseases as discussed above. While it is generally accepted that humans possess a core gut bacterial microbiome, it is still unclear whether a similar core gut mycobiome exists, especially given that fungi are reported to contribute to less than 1% of the microbes in the human gastrointestinal tract (Arumugam et al., 2011; Qin et al., 2010). In fact, a recent survey of the human gut mycobiome in the Human Microbiome Project (HMP) cohort reports both high inter- and high intra-subject variability as opposed to their bacterial counterparts, suggesting the potential lack of a core gut mycobiome in humans (Nash et al., 2017). The observed variability of the gut mycobiome could suggest a high functional redundancy among fungal gut residents, or could be due to stochastic or technical artifacts arising from the low absolute abundance of fungi in human stool. While further work is required to more confidently distinguish these possibilities, it is also important to understand factors that impact the mycobiome composition in order to appreciate its role in the pathogenesis of disease and to develop strategies to maintain and restore a healthy host–mycobiome relationship.

### 3.1 | Host genetics

While there have been to date no systematic studies examining the impact of host genetics on the mycobiome, several studies have detected significant associations between specific genetic variants in the host and the composition of the bacterial microbiome in humans (Goodrich, Davenport, Waters, Clark, & Ley, 2016; Kurilshikov, Wijmenga, Fu, & Zhernakova, 2017). It is therefore likely that the composition of fungal symbionts is similarly influenced by host genetics. Indeed, various genetic immunodeficiencies in humans have been associated with impaired mucosal immunity to symbiotic fungi and consequent fungal outgrowth (Table 3). For instance, individuals afflicted with mutations that diminish the generation of Th17 responses typically suffer from an overgrowth of *Candida* species at various mucosal sites, including the skin, nails, oral cavity, and genital mucosa (Patel & Kuchroo, 2015). Similar diseases involving a bloom of resident fungi have also been observed for mutations in genes involved in fungal sensing. Patients carrying loss-of-function mutations in *CLEC7A* or *CARD9* often suffer from recurrent vulvovaginal candidiasis (RVVC) and *Candida* outgrowth in the nails. In mice, genetic ablation of another fungi-sensing receptor, dectin-3 (*Clec4d*), results in an overabundance of *C. tropicalis*, while a deficiency in mannose binding lectin (MBL) increases the colonization of the intestines by *C. albicans* (Choteau et al., 2016; Wang et al., 2016). Interestingly, two different SNPs in *MBL2* that correlate with diminished MBL levels are also associated with an increased risk of CD and RVVC (Bak-Romaniszyn et al., 2011; Nedovic et al., 2014). Finally, the NLRP3 inflammasome is activated in response to cellular damage provoked by *C. albicans* hyphae and is required for protection in mouse models of vaginal candidiasis. Accordingly, polymorphisms in *NLRP3* are associated with susceptibility to RVVC in women (Jaeger et al., 2016; Lev-Sagie et al., 2009).

While many of the aforementioned genetic variants are associated with the overgrowth of a single fungal species, typically that from the *Candida* genus, their impact on the mycobiota at large remains poorly understood. Nonetheless, limited studies in mice and humans have suggested a broader influence of host genetic mutations on the composition of the symbiont fungi. Patients lacking *STAT3* manifest an increased diversity of their skin mycobiota, which is dominated by *Aspergillus* in addition to *Candida* species (Oh et al., 2013), while *Card9*-KO mice harbor an intestinal mycobiota that is distinct from that of their wildtype counterparts (Lamas et al., 2016). Taken together, the evidence supports a role for host genetics in shaping the mycobiome in much the same way it modifies the bacterial microbiome.



TABLE 3 Human mutations affecting the mycobiota

Gene	Immunological defects	Disease	Sites affected	Mycobiota changes	References
<i>AIRE</i>	Neutralizing autoantibodies against IL-17A, IL-17F, IL-22, resulting in defective Th17 responses; rampant autoimmunity due to defects in negative selection of autoreactive T cells	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, chronic mucocutaneous candidiasis (CMC)	Skin, nails, oral, vagina	<i>Candida</i> overgrowth	Kisand et al. (2010), Puel et al. (2010)
<i>STAT1</i>	Defective Th1 and Th17 responses	CMC	Skin, nails, oral	<i>Candida</i> overgrowth	L. Liu et al. (2011); van de Veerdonk et al. (2011)
<i>STAT3</i>	Defective Th17 responses	CMC	Skin, nails, lungs	Outgrowth of <i>Candida</i> and <i>Aspergillus</i>	Ma et al. (2008), Plantinga et al. (2009)
<i>ACT1</i>	Defective Th17 responses	CMC	Skin, nails, oral, vagina	<i>Candida</i> overgrowth	Boisson et al. (2013)
<i>IL17F, IL17RA</i>	Defective Th17 responses	CMC	Skin, nails, oral, vagina	<i>Candida</i> overgrowth	Puel et al. (2011)
<i>RORC</i>	Defective Th17 and Th1 responses	CMC	Skin, nails, oral, vagina	<i>Candida</i> overgrowth	Okada et al. (2015)
<i>IL12B, IL12RB1</i>	Defective Th17 and Th1 responses	CMC	Skin, nails, oral, vagina	<i>Candida</i> overgrowth	de Beaucoudrey et al. (2010), Ouederni et al. (2014), Prando et al. (2013)
<i>CLEC7A</i>	Defective sensing of beta-glucans and IL-1 $\beta$ /IL-17 production	CMC	Skin, nails, vagina	<i>Candida</i> overgrowth	Carvalho et al. (2012), Plantinga et al. (2009)
<i>CARD9</i>	Impaired dectin-1 and dectin-3 signaling; reduced Th17 responses	CMC	Skin, nails, vagina	<i>Candida</i> overgrowth	Drewniak et al. (2013), Glocker et al. (2009)

## 3.2 | Development and sex

### 3.2.1 | Development

Besides host genetics, age-related differences have also been observed in the human mycobiota, and these are especially distinct in neonates. Cross-sectional studies reveal that newborn infants between 1 and 4 months of age have a gut intestinal mycobiota dominated by *Malasseziales* (*Malassezia*) and *Saccharomycetales* (*Saccharomyces*). Older infants, on the other hand, carry a reduced *Malasseziales* footprint while retaining *Saccharomycetales* (*Saccharomyces* and *Candida*), which is the dominant fungal order in healthy adults (Fujimura et al., 2016). Given that *Malassezia* is a genus encompassing many common skin fungal species, the prevalence of such fungi in young infant intestinal mycobiotas suggests that vertical transmission from the mother might be at play during childbirth and breastfeeding. Indeed, a study compared the similarity of *Malassezia* species between the infants' mycobiotas and those of their respective mothers and observed *Malassezia* colonization in all 27 infants as early as a single day after birth (Nagata et al., 2012). The infants' *Malassezia* profiles subsequently matured to match those of their mothers by day 30 (Nagata et al., 2012). Previous studies have also observed both horizontal and vertical transmission of *Candida* species in infants, of which *C. albicans* is the species most often transmitted vertically (Bliss, Basavegowda, Watson, Sheikh, & Ryan, 2008; Waggoner-Fountain et al., 1996).

While bacterial diversity expands with age in humans presumably due to increased exposure from diet or the environment (Yatsunencko et al., 2012), the human gut fungal diversity has been observed to contract in parallel (Strati, Di Paola, et al., 2016). An orthogonal study in neonates and young infants also confirmed the inverse relationship between bacterial and fungal diversity (Fujimura et al., 2016). It is known that antibiotics treatment results in the outgrowth of the gut mycobiota, probably as a result of reduced ecological competition. While it is tempting to link weaker bacterial competition, especially in infants wherein the bacterial microbiota is less resilient (Koenig et al., 2011; Lozupone, Stombaugh, Gordon, Jansson, & Knight, 2012), to the increase in gut fungal diversity, further work is required to determine if these changes in bacterial diversity is a contributor to or a consequence of reduced intestinal fungal richness in adults.

### 3.2.2 | Sex

Besides age, sex-dependent differences have been reported in the human intestinal mycobiota. A recent cross-sectional study on a cohort of healthy Italian volunteers reported both higher number of fungal isolates and significantly different fungal species in females, and that the female mycobiota is observed to cluster separately from the male mycobiota (Strati, Di Paola,

et al., 2016). It is possible that such differences can be attributed to sex hormones modulating the microbiota composition, as has been previously reported in mice (Markle et al., 2013), or to dietary differences influencing the microbiota make-up in a sex-dependent manner (Bolnick et al., 2014).

### 3.3 | Diet, lifestyle, and seasons

#### 3.3.1 | Diet

The relationship between diet and the mycobiome in healthy individuals has been explored in several studies. There have been multiple reports of fungi detected in fecal samples known to be associated with food, such as *Debaryomyces hansenii* in high-salt fermented foods, and *Penicillium roqueforti* in blue cheese (Hallen-Adams, Kachman, Kim, Legge, & Martínez, 2015). It has been postulated that high levels of *Saccharomyces* in the human gut could be attributed to the consumption of yeast-containing products such as bread and beer. In fact, it has been shown that the level of *S. cerevisiae* in human stools is reduced to undetectable levels upon consuming a *S. cerevisiae*-free diet (Auchtung et al., 2018). Similarly, *Candida* abundance is found to be strongly associated with recent ingestion of carbohydrates (Hoffmann et al., 2013). In a controlled study where participants were placed on plant- or animal-based diets rich in *Penicillium* or *Candida* species, respectively, there were concordant blooms of the respective fungi in the subjects' stool samples (David et al., 2014). A similar study in mice also demonstrated a strong positive association of fungal species in mouse chows with those detected in the murine feces (Iliev et al., 2012). While some of these foodborne fungi found in the gut microbiota might simply be passenger species or transient colonizers, it is generally appreciated that the diet can also serve as a source of several fungal species that can stably colonize the mammalian gut. In fact, a recent study showed that mice fed with a high-fat diet carried significantly different gut fungal communities than those fed with standard chow (Heisel et al., 2017), similar to previous reports on bacterial microbiomes in mice consuming a high-fat diet (Ley et al., 2005; Turnbaugh et al., 2006). Altered mycobiomes have also been observed in humans, as a result of dietary changes and between obese and lean subjects (Mar Rodriguez et al., 2015), suggesting that diet does influence the human gut fungal community structure.

#### 3.3.2 | Lifestyle

The influence of residence, lifestyle, culture and nationality is a huge topic of interest in microbiome research because dietary habits and other environmental exposures can potentially be acted upon to shape the gut and skin microbial composition. In fact, the levels of *C. albicans* in stools have been shown to correlate with the frequency of teeth cleaning (Auchtung et al., 2018). Cross-cultural and cross-national microbiome studies have been conducted on children and adults from Western societies and rural nonindustrialized regions, such as the Amazonas of Venezuela, the uncontacted Amerindians, and people from rural Africa, Papua New Guinea, and Malawi (Angebault et al., 2013; Clemente et al., 2015; De Filippo et al., 2010; Martinez et al., 2015; Yatsunenko et al., 2012). The general consensus is that modern Western societies have a reduced gut and skin microbiota diversity compared to that of populations living traditional agrarian lifestyles. Most of these studies are focused on the bacterial microbiome, but a longitudinal study on the gut mycobiome of Wayampi Amerindians revealed a significantly lower prevalence of *C. albicans* compared to their Western industrialized counterparts; despite a high rate of overall gut intestinal mycobiota carriage and a relatively rich fungal diversity (Angebault et al., 2013). Further work is required to confirm these findings and systematically address the human mycobiome composition in industrialized nations and isolated rural regions.

#### 3.3.3 | Seasonality

Human immune responses undergo significant circannual oscillations (Dopico et al., 2015; Ter Horst et al., 2016). Moreover, seasonality is known to influence people's diet and lifestyle. Together, these seasonal effects could potentially modulate gut microbiome composition in turn. A recent longitudinal study on the microbiome of Hadza hunter-gathers in western Tanzania revealed an annual cyclic change of the gut bacterial microbiome (Smits et al., 2017). In fact, the composition of the Hadzas' microbiome began to resemble that of Western subjects as the dry season, during which meat consumption was highly elevated, approached. This suggests that the shifts in the microbiome observed in industrialized Western nations might not be permanent and that they might be reversible by changes in dietary habits. While this study focused on the bacterial members of the microbiome, it is very likely that fungal diversity could be similarly impacted. Further work is required to thoroughly assess and appreciate the contribution of diet, lifestyle and seasonality to the diversity and function of the human mycobiome.

### 3.4 | Bacterial microbiota

Fungal overgrowth has been observed as a result of antibiotic treatment in experimental animals, healthy humans, and neutropenic patients. The current view posits that a healthy bacterial microbiota may control *Candida* and other fungal populations.

For instance, healthy mice are generally resistant to *C. albicans* colonization in the gut, but this resistance is lost upon broad-spectrum antibiotics treatment (Fan et al., 2015). RVVC, a common condition affecting a large number of women (Blostein, Levin-Sparenberg, Wagner, & Foxman, 2017), has been linked to antibiotics usage (Leegaard, 1984; Spinillo, Capuzzo, Acciano, De Santolo, & Zara, 1999; Xu et al., 2008). It is believed that antibiotics lead to the depletion of protective lactobacilli generally found in the vaginal microbiota (Ravel et al., 2011) and a change in the vaginal pH that collectively permit yeast overgrowth.

Both examples suggest the presence of bacterial–fungal interactions that cannot simply be attributed to competition for host surfaces and nutrients alone (Cottier & Pavelka, 2012; Peleg, Hogan, & Mylonakis, 2010). Several synergistic interactions have been reported between bacteria and fungi, mainly with regards to *C. albicans*. Bacterial peptidoglycan-derived subunits found in human serum have been demonstrated to be potent inducers of hyphal growth in *C. albicans* (Xu et al., 2008). Furthermore, *Pseudomonas aeruginosa* and *Escherichia coli* are known to increase *C. albicans* virulence and subsequent lethality in various murine models (Gale & Sandoval, 1957; Neely, Law, & Holder, 1986). *Staphylococcus epidermis*, an organism commonly isolated in catheter-associated infections, can form polymicrobial biofilms together with *C. albicans*, which are resistant to both vancomycin and fluconazole (Adam, Baillie, & Douglas, 2002).

Nonetheless, antagonistic bacterial–fungal interactions are more frequently reported. Members of the bacterial microflora produce weak organic acids via fermentation of complex carbohydrates (Mortensen & Clausen, 1996) and these acids exert a fungistatic effect on *C. albicans* (Cottier, Tan, Xu, Wang, & Pavelka, 2015; Noverr et al., 2004). Besides secreting lactic and acetic acid, vaginal lactobacilli produce reactive oxygen species, such as hydrogen peroxide (Fitzsimmons & Berry, 1994), and biosurfactants like surlactin (Velraeds, van de Belt-Gritter, van der Mei, Reid, & Busscher, 1998), both of which inhibit *C. albicans* growth. *Enterococcus faecalis* and *C. albicans* antagonize each other's virulence in in vitro biofilm models and in murine oropharyngeal infection models (Cruz, Graham, Gagliano, Lorenz, & Garsin, 2013). Specifically, *E. faecalis* secretes a bacteriocin, EntV, that inhibits the in vitro biofilm formation and virulence of *C. albicans* in a murine oropharyngeal infection model by blocking hyphal morphogenesis (Graham, Cruz, Garsin, & Lorenz, 2017). *P. aeruginosa* also limits hyphal development in *C. albicans* by secreting a quorum-sensing molecule (QSM), 3-oxo-C12-homoserine lactone (Hogan, Vik, & Kolter, 2004). Similar QSMs (diffusible signal factor) have been discovered in *Burkholderia cenocepacia* and *Burkholderia cepacia* (Boon et al., 2008). Besides blocking hyphal formation, *P. aeruginosa* also binds to *C. albicans* hyphae, forms biofilms, and kills *Candida* through the secretion of hemolytic phospholipase C, which degrades phosphatidylcholine abundant in eukaryotes, and of redox-active phenazines that generate highly toxic reactive oxygen species (Gibson, Sood, & Hogan, 2009; Hogan & Kolter, 2002). While most examples are *Candida*-centric, there are few but growing reports of antagonistic interactions between bacteria and other fungi. For instance, both *P. aeruginosa* and *S. aureus* are known to inhibit *A. fumigatus* biofilm formation (Mowat et al., 2010; Ramirez Granillo et al., 2015).

Given that bacteria both promote virulence via peptidoglycan shedding and inhibit growth and hyphal development via the secretion of SCFAs and QSMs, respectively, it is challenging to predict whether the net effect of a specific consortium of bacterial species at a particular host site will be to facilitate or to inhibit fungal infections. Indirect, for example, host-mediated, effects further compound the complexity of the contribution of the bacterial microbiota on fungal diversity. In mice, different symbiotic bacterial phyla block *C. albicans* gut colonization indirectly via HIF-1 $\alpha$  activation and subsequent secretion of antimicrobial peptides from gut epithelial cells (Fan et al., 2015). In addition, bacteria are reported to metabolize tryptophan into metabolites that act as Ahr ligands, which in turn contribute to an Ahr-dependent IL-22 mucosal response, allowing the survival of bacteria while resisting *C. albicans* colonization (Lamas et al., 2016; Zelante et al., 2013). Both examples clearly illustrate the importance of considering bacterial–fungal interactions within the context of a complex and dynamic host environment.

## 4 | HOW WE CAN STUDY THE MYCOBIOME?

The relative impact of factors influencing the composition and functionality of the mycobiome, and how these might contribute to the commensalism-pathogenicity switch in certain fungi such as *Candida*, remains largely unresolved. More research is therefore required to understand the mycobiome in the context of human health and disease, and the first step towards this goal is to establish consensus methodologies in mycobiome research to facilitate comparative analysis across different studies.

### 4.1 | Culture-dependent methods

The gold-standard method of fungal identification is to culture them on solid or in liquid antibiotics-supplemented media and evaluate the species by analyzing the morphology of colonies or of actively dividing cells. It is the unambiguous method for detecting live fungi, although unsuccessful culturing does not necessarily demonstrate the absence of viable fungi.

Unfortunately, many fungi cannot be cultivated; hence relying solely on culture-dependent methods to characterize the viable portion of mycobiotas is not possible at present. Moreover, these methods are poor at detecting low-abundance species, unless one has a target species in mind and a strategy to selectively enrich for it. Unsurprisingly, previous mycobiome studies using culture-dependent methods consistently reported a significantly lower diversity than culture-independent analyses (Chen et al., 2011; Delhaes et al., 2012; Ghannoum et al., 2010; Hamad et al., 2017), identifying less than 30% of the fungal species reported in the human gut (Hamad et al., 2017; Hamad, Raoult, & Bittar, 2016). Nevertheless, these methods remain highly valuable for assessing inter- and intra-species phenotypes such as growth, cell morphology, drug resistance and other host adaptation traits (S. H. Kim et al., 2015; Strati, Di Paola, et al., 2016).

## 4.2 | Culture-independent methods and their challenges

Culture-independent methods circumvent the preceding problems by identifying fungi directly from their genomic DNA or RNA content, but present a new set of constraints and challenges.

### 4.2.1 | Fungal viability cannot be unequivocally established

It is important to point out that sequencing methods are ultimately agnostic to viability status of the analyzed microbial cells, since extracellular nucleic acids derived from dead cells can persist in the environment and cannot be differentiated from those in live organisms. Without selective detection of live microbes, sequencing methods, especially DNA-based approaches, can potentially inflate the type and number of viable taxa detected in microbial communities (Carini et al., 2016). However, RNA is significantly less stable than DNA, and can thus be used to differentiate viable or recently active microbes from metabolically inactive or dead ones. In any case, culture-independent sequencing methods can readily provide a detailed resolution of fungal community profile and function that is unattainable with current culture-based methods, and are therefore essential complementary approaches in mycobiome studies.

### 4.2.2 | Efficient genomic content isolation is crucial

All sequencing-based methods require efficient and unbiased extraction of nucleic acids to obtain the true diversity and abundance of fungal communities. While genomic content extraction methods have been developed for bacteria in microbiome analyses, they are generally inefficient for fungi due to the nature of their rigid cell walls, which cannot be easily lysed. A recent study evaluating DNA extraction methods from saliva samples demonstrated that diversity of fungi, unlike that of their bacterial counterparts, is heavily influenced by the method employed (Vesty, Biswas, Taylor, Gear, & Douglas, 2017). Based on our experiences and other comparative studies of DNA extraction methods (Halwachs et al., 2017; Huseyin, Rubio, O'Sullivan, Cotter, & Scanlan, 2017), at least an extra bead-beating step is required to ensure mechanical lysis of fungal cell walls for effective genomic content recovery. The best practices for culture-dependent and -independent methods are covered in greater depth elsewhere (Huseyin et al., 2017).

## 4.3 | Fungal detection methods often do not converge to the same result

Following DNA isolation, different methods of detecting and characterizing fungal DNA can often lead to different results. Direct shotgun sequencing of the genomic DNA, or metagenomics, is the most unbiased approach, for it detects viruses and all other microbes present in the sample. By virtue of their nonspecificity, however, metagenomic approaches are sensitive to host DNA contamination, which can easily dominate most of the sequencing reads in saliva samples and samples collected from soft tissues, such as the vagina, anterior nares or throat (Human Microbiome Project Consortium, 2012). This is especially critical for mycobiota studies since fungi occupy a small but important fraction of the microbiome, ranging from 0.03% in the gut to ~10% on the skin (Belkaid & Segre, 2014; Ott et al., 2008; Qin et al., 2010). Moreover, metagenomic approaches require a high sequencing depth to obtain an accurate fungal signature, and are therefore prohibitively expensive for large-scale studies (Cottier et al., 2018).

Most mycobiome studies generally employ fungal-specific amplicon-based sequencing, which is affordable and eliminates the problem of host DNA contamination. Amplicon-based sequencing also holds the promise of detecting rare fungal species, so long as the primers can efficiently target their fungal DNA. However, caution should be taken, for polymerase chain reaction (PCR) amplification occurs in a nonlinear manner and is intrinsically biased towards smaller target regions. The choice of target template also matters: the highly conserved 18S ribosomal DNA (rDNA) region is often used to quantify the total fungal abundance (C. M. Liu et al., 2012), while either of the two hypervariable fungal rDNA internal transcribed spacer (ITS) regions, ITS1 or ITS2, can be used for taxonomic identification of the various fungal species in a sample (Schoch et al., 2012).

Even the choice of the hypervariable ITS region as a universal fungal thumbprint suffers from several constraints. First, several unique fungi share identical ITS regions, such as the *Pezizomycotina* genera with shorter ITS barcodes (O'Donnell &

Cigelnik, 1997; Schubert et al., 2007; Skouboe et al., 1999), such that additional markers are required to discriminate between these species. Second, ITS regions are present in multiple copies within a fungus (Kiss, 2012) and ITS copy numbers vary enormously between and within fungal species, rendering it close to impossible to determine the true abundance of any fungal species. In addition, intragenomic variation such as multiple paralogous or nonorthologous ITS copies within a single species may contribute to the overestimation of overall fungal diversity (Schoch et al., 2012). The highly variable length of ITS regions across fungi also contributes to biases in PCR amplification and sequencing (Schoch et al., 2012; Tang, Iliev, Brown, Underhill, & Funari, 2015). Lastly, like bacterial 16S ribosomal RNA (rRNA) sequencing, there is no single ITS primer combination that can amplify all fungal species (Bellemain et al., 2010), thus necessitating the use of multiple primers and/or of partially degenerate primers to capture the complete fungal diversity. Despite these limitations, ITS is still considered a standard marker for distinguishing phylogenetically more distant fungal species and ITS amplicon-based sequencing is generally used in most mycobiome studies due to its low cost and reasonable sensitivity.

Our research group has recently developed an approach known as meta-total RNA sequencing (MeTRS), which employs the same principle as metagenomics sequencing except that it relies on shotgun analysis of total RNA, as opposed to genomic DNA (Cottier et al., 2017). Like metagenomics, it potentially detects all viruses (except latent ones) and other microbes, and might suffer from host RNA contamination, given the unbiased nature of the method. However, in stool samples where host cell contamination is less of an issue compared to other host tissues, total RNA sequencing emerges to be more sensitive than metagenomics in the detection of fungi. This was shown to be due to the RNA content per fungal cell to be substantially higher than that in bacteria, therefore requiring significantly less sequencing depth (Cottier et al., 2017). This unbiased interrogation of complex microbial communities and the relatively lower sequencing depth requirements endow MeTRS with the potential of a broad application in large-scale microbiome profiling studies and to deepen our knowledge of the human mycobiome.

#### 4.3.1 | Fungal identification accuracy is constrained by the quality of reference databases

After sequencing, researchers have to decipher the identity of the organisms hidden within this sequence information. The bioinformatic analysis consists of multiple steps, and the choice of methods and parameters employed in each step heavily influences the final fungal community profile. A more detailed critical review of the bioinformatic workflow was recently published (Halwachs et al., 2017). Regardless of the methods used, accurate fungal identification from sequence information requires reference databases of high quality. While the analysis of bacteria 16S or metagenomics profiles is facilitated by many high-quality reference databases, there are few such well-established databases for fungi-targeted sequencing. Furthermore, even though fungi, with an estimated 1.5 million species, represent one of the largest branches of the Tree of Life, the number of high-quality fungal sequences in databases such as SILVA for rRNA sequences (Pruesse et al., 2007) or UNITE for ITS sequences (Abarenkov et al., 2010) is significantly fewer than that of available bacterial rRNA sequences. In addition, even a hit might give rise to discrepancies across fungal databases because there is currently no unified consistent nomenclature at the higher taxonomic levels and name changes occur frequently at every level (Hibbett et al., 2007). Confounding redundancies are also common in fungal databases, since many fungi have sexual and asexual forms and are consequently misidentified as two different taxa assigned even to different families (Halwachs et al., 2017).

#### 4.4 | Bottom-up approaches

Mycobiome studies are currently focused on the characterization of entire fungal communities residing in healthy and diseased subjects, and are starting to establish that numerous diseases are associated with alteration in the abundance of specific members of the mycobiota. While these top-down approaches are advantageous in the determination of simple host–microbe interactions, most host–microbe relationships are the result of many complex and dynamic microbe–microbe and microbe–host interactions where the host environment is in a constant state of flux. In light of these challenges, attempts have been made to further understand these relationships using bottom-up approaches through the study of pairwise interactions in vitro using model microorganisms or in vivo via monocolonization in germ-free animals. Understanding pairwise competitive and cooperation outcomes (Gore, Youk, & van Oudenaarden, 2009) will allow for the prediction of survival when these pairs are placed in within the context of a larger number of species (Friedman, Higgins, & Gore, 2017). At the same time, studying fungal monocolonization can reveal unexpected, new aspects of fungal biology: *C. albicans* in monocolonized mice has been observed to adopt a commensal-like yeast-cell form, as opposed to a morphologically heterogeneous population observed in antibiotics-treated mice (Bohm et al., 2017).

Besides the reductionist pairwise mode of inquiry, there are also ongoing attempts to study simplified microbial communities or to recapitulate host physiological environments in ex vivo systems. Building and maintaining simplified microbial communities such as fermented foods or other synthetic communities of intermediate diversities will provide hypotheses, techniques, and strategies for understanding and manipulating more complex microbiomes (Wolfe, Button, Santarelli, &

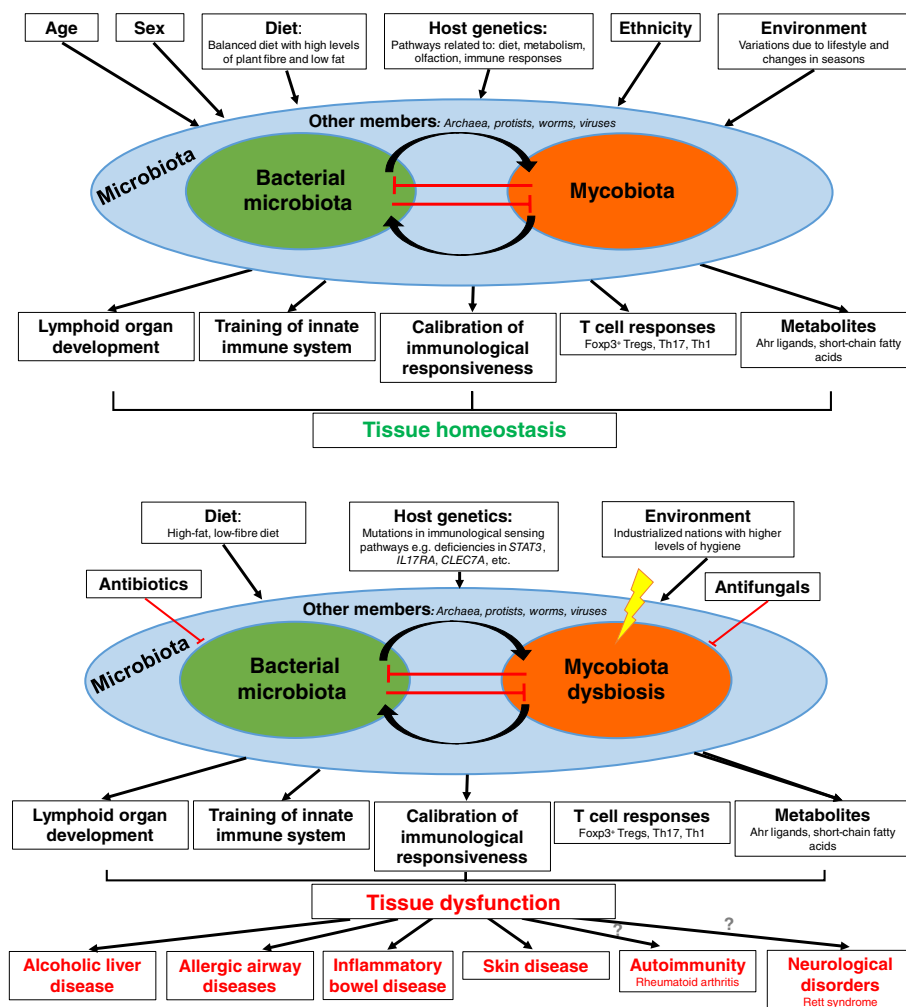


Dutton, 2014; Y. Zhang, Kastman, Guasto, & Wolfe, 2018). Recapitulating host physiological environments using microfluidic tissue cultures and organoids can potentially illuminate spatial–temporal mechanisms by which commensal and pathogenic bacteria contribute to both local and long-ranged host immune responses while allowing tight experimental control (H. J. Kim, Li, Collins, & Ingber, 2016; VanDussen et al., 2015; Yissachar et al., 2017).

On the theoretical front, both mathematical and agent-based modeling approaches have been employed to explain observational data and generate predictions in a defined *in silico* ecosystem. Game-theoretical methods have been applied to understand microbial models of cooperation and competition (Gore et al., 2009) and host–microbe interaction models (Tyc et al., 2016), while agent-based modeling of *Candida*, microbiota, neutrophils, and macrophages have revealed potential synergistic-treatment combinations against *Candida* infections (Tyc et al., 2016). Overall, these concerted experimental and theoretical efforts can help to improve our understanding of microbial communities while establishing tractable model communities to test ideas from theoretical ecology and empirical observations.

## 5 | CONCLUSION

It is now evident that fungi form a crucial component of mammalian microbiotas and fungi, like their bacterial counterparts, contribute to diverse facets of human health, particularly in the context of host immunological homeostasis. At the same time, the composition and function of the mycobiota can be modulated by an assortment of factors, ranging from host genetic variation to diet to influences from the bacterial microbiota. A combination of perturbations to the mycobiota—arising from genetic



**FIGURE 1** Host genetic and nongenetic factors, including trans-kingdom microbe–microbe interactions, collectively influence the composition of the microbiota (which subsumes the mycobiota, symbiotic bacteria, and other microbes such as viruses) at various barrier sites of the body. In healthy people, the mycobiota modifies host physiology, in particular host immunity, in a variety of ways, and contributes to tissue homeostasis (upper panel). A combination of perturbations, including genetic mutations in the host and the use of antibiotics or antifungals, may disrupt the mycobiota sufficiently to provoke pathological tissue function, excessive inflammation, and ultimately disease (lower panel), although the etiological links between fungal dysbiosis and pathology remain to be verified for certain skin, autoimmune, and neurological diseases (indicated by a question mark “?”)

mutations in the host, the prolonged use of antibiotics, the consumption of foods deficient in plant-based complex carbohydrates, and so on—might suffice to disrupt normal tissue function and provoke over-exuberant inflammation and disease (Figure 1). Future studies will yield fresh insights into the interactions between the mycobiota, symbiotic bacteria and the host, and guide ongoing endeavors to manipulate our microbiotas to enhance health and mitigate disease. To that end, we will need to improve upon existing technologies and analytics, to identify and characterize fungal species with greater accuracy and coverage.

Beyond tool development, identifying members of the mycobiota that are responsible for host immunological homeostasis or disease pathogenesis will be vital to advancing the field. This cannot simply be achieved by mycobiome-wide association studies alone. As we move forward, the importance of merging unbiased top-down and targeted bottom-up systems biology approaches will be of ever-increasing importance, to allow us to advance from community structure characterization to functional annotation, as well as from association to causation. Recent work by Surana & Kasper (2017) describe one such strategy that may help to demonstrate causal roles between microbes and host phenotypes via microbe–phenotype triangulation, wherein highly related microbial communities yielding distinct or intermediate host phenotypes are compared to reveal the microbe(s) whose abundance is correlated with the observed phenotype (Surana & Kasper, 2017). Applying strategies like this will enable us to move from laundry lists of microbes implicated as biomarkers of disease to tractable models providing insight into how host and microbial responses affect the mycobiome and vice versa during diseased states, and correspondingly inform better clinical strategies to promote or modify microbiota states to fight infection, and eventually manage human health.

## GLOSSARY

Commensalism	A symbiotic relationship whereby one organism benefits from another without causing deleterious effects to the other (Johnson, Graham, & Smith, 1997). Derived from the Latin word “commensalis,” meaning “table companion”
Diversity (herein used as a synonymous of $\alpha$ -diversity)	The number of different species that are represented in a given ecological community. Species diversity takes into account both species richness (how many different species are present) and species evenness (how similar the relative abundances of the different species are)
Dysbiosis	A pathological deviation from the normal microbiota composition on or inside the body (Tamboli, Neut, Desreumaux, & Colombel, 2004)
Microbiome	The entire habitat, including the microorganisms, their genomes, and the surrounding environmental conditions (Marchesi & Ravel, 2015)
Microbiota	The complex and diverse community of microorganisms that live in symbiosis with a given host
Mycobiome	The collective genomes of a mycobiota (Ghannoum et al., 2010)
Mycobiota	The community of fungi that lives in symbiosis with a given host
Pathobiont	A symbiont that normally does not damage the host but under particular conditions has the potential to inflict damage and to cause disease (Mazmanian, Round, & Kasper, 2008)
Pathogenicity	The capacity of a microbe to cause damage in a host (Casadevall & Pirofski, 1999). Derived from the Greek word “pathos,” meaning “suffering”
Symbiosis	A close long-term relationship that occurs between dissimilar species. Derived from Greek, meaning “living together”
Virulence	The relative capacity of a microbe to cause damage in a host (Casadevall & Pirofski, 1999)

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## CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

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