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The human gut mycobiome: pitfalls and potentials—a mycologist's perspective

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Abstract: We have entered the Age of the Microbiome, with new studies appearing constantly and whole journals devoted to the human microbiome. While bacteria outnumber other gut microbes by orders of magnitude, eukaryotes are consistently found in the human gut and are represented primarily by the fungi. Compiling 36 studies 1917–2015 we found at least 267 distinct fungal taxa have been reported from the human gut, and seemingly every new study includes one or more fungi not previously described from this niche. This diversity, while impressive, is illusory. If we examine gut fungi, we will quickly observe a division between a small number of commonly detected species (*Candida* yeasts, *Saccharomyces* and yeasts in the Dipodascaceae, and *Malassezia* species) and a long tail of taxa that have been reported only once. Furthermore, an investigation into the ecology of these rare species reveals that many of them are incapable of colonization or long-term persistence in the gut. This paper examines what we know and have yet to learn about the fungal component of the gut microbiome, or "mycobiome", and an overview of methods. We address the potential of the field while introducing some caveats and argue for the necessity of including mycologists in mycobiome studies.

Key words: *Candida*, human health, microbiome, next-generation sequencing

Introduction

All surfaces of the human body exposed to the environment are colonized with complex and diverse populations of microorganisms from all three domains of life (Clemente et al. 2012). A majority of the microbes colonizing the human host reside within the gastrointestinal (GI) tract, making the GI tract home to one of the densest microbial communities on Earth. Approximately 100 trillion microorganisms inhabit the human gut and outnumber human host cells by a factor of 10 to 1 (Whitman et al. 1998). This population of microbes, collectively termed the gastrointestinal microbiota, has received much attention and has been at the forefront of biological research for the past decade.

Microbial numbers increase in a gradient from the stomach to the colon (Schulze and Sonnenborn 2009). The upper gastrointestinal tract (stomach, duodenum, jejunum, proximal ileum) contains a relatively low number of microorganisms. Few organisms ($<10^2$ cells/mL), consisting of acid-tolerant lactobacilli and streptococci, are present in the stomach and upper small intestine due to harsh pH conditions (Mackie et al. 1999). Cell densities in the proximal small intestine are 10^4–10^5 cells/mL of intestinal content (Walter and Ley 2011). The lower gastrointestinal tract (distal ileum, colon) contains a much higher population and diversity of microorganisms—10^8 cells/gram in the distal ileum and approaching 10^{10}–10^{12} cells/gram in the colon. Higher pH, low concentration of bile acids and longer retention due to slower peristalsis are several properties that distinguish the colon from the rest of the GI tract and allow it to be the primary site of colonization (Walter and Ley 2011). This allows easily-collected fecal samples to provide a reasonable snapshot of the gut microbiome.

Bacteria are the most abundant microorganisms in the gastrointestinal tract: more than 99% of the genes in the human gut microbiome are of bacterial origin and the number of bacterial species reported from the gut is generally estimated at 500–1000 (Xu and Gordon 2003, Qin et al. 2010). Current evidence suggests members of the kingdom Archaea reside alongside bacteria in the gut, albeit in much lower numbers (Qin et al. 2010). Two large-scale projects, the Human Microbiome Project and MetaHit, provide an initial compilation of the gut microbiome ecosystem from 242 and 124 humans, respectively (NIH HMP Working Group et al. 2009, Qin et al. 2010, Human Microbiome Project Consortium 2012). One study involving fecal samples from 124 Europeans showed each individual harbored at least 160 species of bacteria and a majority of the species was shared among individuals (Qin et al. 2010). As revealing as the results have been, studies to date from these projects focused exclusively on the bacterial component and other kingdoms were not considered. Smaller-scaled, fungal-specific studies using culture-dependent and/or culture-independent methods thus have been conducted but are limited.

Eukaryotes in the human gut are less extensively studied than prokaryotes, yet remain an important component of the microbiome. The protist *Blastocystis* and fungi (as a group) both have been reported as

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the dominant eukaryotes in the gut (Rajilic-Stojanovic et al. 2007, Nam et al. 2008, Scanlan and Marchesi 2008). The term mycobiome was coined in 2010 to differentiate the fungal biota from the bacterial biota, in that the word "microbiota" is frequently treated as synonymous with bacteria (Ghannoum et al. 2010). On 6 Jul 2013, using a PubMed search, the word "mycobiome" appeared in the literature 10 times (Cui et al. 2013), while a 7 Jun 2015 search yielded at least 38 "mycobiome" studies. "Mycome", coined in 2014 (Ianiro et al. 2014), also has been suggested.

Every human being is colonized with fungi, and fungal populations colonize the human host at multiple body sites—gastrointestinal tract, oral cavity, skin, vaginal tract and lungs (Ghannoum et al. 2010, Drell et al. 2013, Findley et al. 2013, Hoffmann et al. 2013, Huffnagle and Noverr 2013, van Woerden et al. 2013). Different fungi are associated with different body sites, with the skin harboring near-monotypic assemblages dominated by *Malassezia* species, while the most diverse assemblages are found in the oral cavity and gastrointestinal tract (Underhill and Iliev 2014). Many human-associated fungi are opportunistic pathogens in that disease is caused when the host defense system becomes weakened. Well-known fungal infections range from skin mycoses such as athlete's foot, ringworm and yeast infections to life-threatening systemic mycoses caused by *Cryptococcus*, *Candida*, *Aspergillus*, *Coccidioides* and *Pneumocystis*. An estimated 75% of women will suffer a yeast infection during their lifetime and roughly 20–25% of the world's population has skin mycoses (Sobel 2007, Havlickova et al. 2008). Fungi represent the majority of eukaryotes in the human gut microbiome and the remainder of this review will detail and depict what is currently known about the relatively new field of human gut mycology.

GASTROINTESTINAL COLONIZATION BY FUNGI

Gastrointestinal microbial colonization starts at birth. The vaginal tract is home to a large number of yeasts and, not surprisingly, neonates born vaginally are colonized by yeasts from their mother's vaginal microbiota (Bliss et al. 2008). Infant colonization by *Candida* spp. is therefore transmitted vertically from the maternal microbiota and also horizontally from the environment and hands of family members and health care workers (Lupetti et al. 2002, Bliss et al. 2008). The prevalence of *Candida* spp. gut colonization in newborns on the day of birth is roughly 23%, increasing to 50% by 4 mo (Ellis-Pegler et al. 1975, Saiman et al. 2001). Yeast carriage rates in infants are approximately 10^3–10^5 CFU/g feces (Ellis-Pegler et al. 1975, Benno et al. 1984).

Fungi are detectable in all sections of the GI tract of about 70% of healthy adults, normally at up to 10^3 fungal cells per mL or g of intestinal contents (Schulze and Sonnenborn 2009). Culture-independent analyses show fungal genes constitute less than 0.1% of the human gut microbiome (Qin et al. 2010). The low abundance of fungi in the gut microbiome undoubtedly relegates them to part of the "rare biosphere" (Sogin et al. 2006). The rare biosphere is of significance in that it potentially serves as a reservoir for pathogens or keystone species that have a critical role in maintaining the structure and function of the human gut microbiome (Huffnagle and Noverr 2013).

The oral cavity, which provides a direct route of entry to the gastrointestinal tract, is asymptomatically colonized by *Candida* and harbors a wide diversity of fungi, likely from food and airborne spores (Arendorf and Walker 1979, Ghannoum et al. 2010). The rapid luminal flow and low pH of gastric acid lets few microorganisms colonize the stomach and functions as a barrier to prevent ingested pathogens from reaching the intestine (Martinsen et al. 2005). A number of acid-resistant bacteria exist in the stomach as well, such as a few acid-tolerant fungi like *Candida* and *Phialemonium* (Bik et al. 2006, von Rosenvinge et al. 2013). The diversity of fungi in the small intestine is largely unexplored due to the difficulty in collecting samples (Wang et al. 2014). Ileal effluent collected from intestinal transplant recipients showed colonization by *Saccharomyces cerevisiae*, *Candida* spp., *Cryptococcus neoformans* and *Aspergillus clavatus* (Li et al. 2012). The properties of the large intestine facilitate extensive microbial colonization and proliferation, and a wide diversity of fungal genes is detected in the lower gastrointestinal tract.

METHODS FOR CHARACTERIZING THE GASTROINTESTINAL FUNGAL COMMUNITY

The first studies taxonomically identifying the fungi of the gastrointestinal tract (as opposed to merely documenting the presence of fungi without identification) date to the early 1900s (Kohlbrugge 1901, Anderson 1917). The ability to culture fungi was critical for identification. At the time it was known that feces contain a large number of bacteria compared to fungi and ordinary culture medium and plating methods would not be sufficient for the isolation of fungi from the gut. Therefore media inhibiting bacterial growth, such as Sabouraud's agar, were commonly used (Ashford 1915, Anderson 1917). Historically identification and classification of yeasts was based on readily observable gross colony features (color, size, shape), microscopic examination and biochemical properties.

Although advances have been made in culture-dependent methods, these methods present several

disadvantages that restrict the ability of mycologists to accurately characterize fungi in fecal samples. In culture-based studies, dominant populations (e.g. *Candida* spp.) can mask the detection and diversity of low-abundance organisms. In addition, current fungal culture techniques may be inadequate to optimally cultivate organisms that require microbe-microbe interactions because culture fails to reproduce ecological niches and symbiotic relationships encountered in the natural environment (Carraro et al. 2011, Beck et al. 2012). The culturable fraction also is distorted because replication times vary among microorganisms and fast-growing species efficiently outcompete others (Nocker et al. 2007).

The development of PCR in the 1980s revolutionized fungal detection methods (Saiki et al. 1985), and high-throughput nucleic acid sequencing has become the preferred method for mycobiome studies (Dollive et al. 2012, David et al. 2014). Sequencing techniques are capable of distinguishing species with genes within the fungal ribosomal RNA gene cluster—18S small subunit rDNA, 28S large subunit rDNA and the internal transcribed spacer (ITS1 or ITS2). rRNA genes are appealing targets for fungal identification because they are highly multicopy in each genome. Fungal rRNA genes have highly conserved regions serving as primer binding sites to determine the sequences of adjacent variable regions by PCR amplification. In fungi 28S provides much greater resolution than 18S and continues to be used for within-genus (i.e. species-level) identification and phylogenetic studies, while 18S is rarely adequate to distinguish species (Das et al. 2014) (in contrast with the analogous bacterial 16S gene, which is widely used for identification). ITS genes are less conserved and therefore are considered the best target for fungal species and subspecies identification (Porter and Golding 2012, Schoch et al. 2012). PCR and sequencing biases exist, notably a bias toward shorter sequences with Illumina MiSeq and especially Ion Torrent methodologies (Tang et al. 2015). Nonetheless next-generation sequencing of these genes has provided the most accurate account of the fungal composition of the human gut microbiome.

Since 2008 the most commonly used methods for identifying gut fungi involve some form of ITS sequencing coupled with a BLAST query, both of which have limitations. ITS sequence is insufficient to differentiate between certain closely related species (e.g. *Alternaria alternata, A. brassicicola* and *A. tenuissima* or *Cladosporium cladosporioides, C. bruhnei, C. herbarum/Davidiella tassiana, C. macrocarpum, C. sphaerospermum* and *C. tenuissimum*), so the exact number and identities of species reported remains undetermined. BLAST results also are subject to the limits of the relevant database, a limitation made clear in a study in which the dominant fungus recovered from the gut had "sequences 100% identical to both *Gloeotinia temulenta* (DQ235697) and *P[aecilomyces] fumosoroseus* (AB086629)" (Scanlan and Marchesi 2008). These GenBank accessions indeed are identical, but the species' ITS sequences are not; one is misidentified. In addition to misidentifications databases may contain multiple names for one organism (especially anamorphs and teleomorphs) or may contain insufficient information to lead to an identification ("soil fungus", "unclassified ascomycete" etc.) (Tang et al. 2015). Efforts are underway to develop and maintain curated sequence databases, and Tang and colleagues (2015) report the development of a targeted host-associated fungi (THF) ITS database specifically for microbiome samples.

Metagenomic sequencing has become common for bacterial microbiome studies and offers the advantage of functional characterization—identifying not only members of the microbiome but also the functions they perform, for example, inulin breakdown or butyrate production (Walter and Ley 2011). To date this approach has not been adopted for fungi, due to the lack of a good, culture-independent, method of separating out fungi from the thousandfold more abundant bacteria. However, genome sequence is available for many of the fungi most likely to be true members of a gut community (e.g. *Candida albicans* and other opportunistic *Candida* species). With the use of such annotated genomes and transcriptomic data, the potential for metagenomic studies to yield valuable information about the activities of particular fungi is high.

A few studies have used a combination of culture-dependent and -independent methods for the identification of gut fungi and compared the results. One study exploring the diversity of gut eukaryotes in a Senegalese man identified 16 fungal species by molecular methods targeting the ITS, 18S and 28S genes and only four fungal species by culturing, using three culture media (Hamad et al. 2012). Three of the four fungi isolated by culture also were detected by sequencing; the exception was *C. krusei*. An earlier study also highlighted a culturing bias. *Candida* spp. were identified as predominant by cultivation methods while "*Gloeotinia/Paecilomyces*" and *Galactomyces* were found to be the predominant species using clone libraries (Scanlan and Marchesi 2008). Chen and colleagues found 37 fungal OTUs using clone libraries while only five species, from two genera (*Candida* and *Saccharomyces*), were isolated on two culture media (Chen et al. 2011). Of interest, two of these five species were not detected by cloning and sequencing, which failed to detect *C. krusei* and *C. glabrata*.

COMPOSITION OF THE GASTROINTESTINAL FUNGAL COMMUNITY

Previous culture-dependent studies identified *Candida* spp. as the most common (if not the only) fungi in the GI tract. With the development of advanced culturing methodologies and PCR, the modern era of mycobiome studies has exposed a more in-depth survey of both culturable and unculturable fungi in the gut. At present only a handful of mycobiome characterization studies exist. We compiled a list of fungal species reported from the GI tract of humans (TABLE I**,** SUPPLEMENTARY TABLE I; include: healthy and diseased adults and infants; fungi from stomach, small intestine, large intestine; differing diets and varying geographic locations), from articles spanning 1917–2015. If a more current name for a fungus exists than that used in the initial study, the current name is also listed. Fungi reported from the literature but not specified to the species are excluded from the list if a species from that genus, family or class is listed (e.g. *Candida* sp., Capnodiales sp.). Fungi that cannot be identified ("unclassified ascomycete", "unclassified fungus") are omitted. Taxa reported in the literature that are indistinguishable from one another at the level of the target gene used are listed in the same row. One list (TABLE I) is limited to those fungi reported in more than one study and is organized by broad ecological categories; a comprehensive, alphabetical list, including those fungi reported only once is provided (SUPPLEMENTARY TABLE I.

The most commonly detected fungi in the GI tract of humans among the 35 studies listed (TABLE I) are *C. albicans* (25 studies), *Saccharomyces cerevisiae* (19), *C. tropicalis* (17), *C. parapsilosis* (13), *C. glabrata* (12), *C. krusei* (10), *Cladosporium cladosporioides* (10), *Penicillium allii* (10), *Malassezia globosa* (8), *M. restricta* (7), *Debaryomyces hansenii* (7) and *Galactomyces geotrichum* (7). *Candida* species are known to dominate the GI tract of humans, and their presence is not surprising. At least 267 distinct fungal taxa have been reported in the gut, which is considerably lower than the estimated 500–1000 bacterial taxa residing therein (Xu and Gordon 2003, Qin et al. 2010). In addition, a majority of the fungi (200; SUPPLEMENTARY TABLE I) were reported only in one study. While approximately 40% of the fungal taxa reported from the gut are yeasts, yeasts represent 63.4% of the taxa reported from multiple studies, and 10 of the 12 most commonly detected fungi are yeasts.

We provide a conservative classification of fungi by niche (TABLE I), in which the classifications come from the literature or frequently the substrate of the type specimen. This classification is broadly correct but subjected to some caveats; for example, the type of *Candida intermedia* was isolated from feces, but every taxon (TABLE I) has been detected in feces, so fecal isolation does not necessarily indicate the primary habitat. Taxa for which the niche is listed as "other" have commonly been isolated from a wide variety of substrates.

Unlike bacteria, for which evidence exists for a "core microbiome" of varying but related species performing a defined set of metabolic functions and ecologic roles, shared by much of the human population (Lozupone et al. 2012), evidence for a stable "core mycobiome" is lacking. A small number of species, largely Saccharomycetalean yeasts, are reported from multiple samples in multiple studies, while more than two-thirds of all reported species are detected only in a single sample and/or study (Hallen-Adams et al. 2015, Suhr 2015; SUPPLEMENTARY TABLE I). The majority (77%) of taxa detected in a single study were detected by nonculture methods, and thus may have been nonviable. An understanding of fungal ecology and physiology suggests that even relatively commonly detected gut fungi (e.g. *Debaryomyces hansenii* and multiple *Penicillium* species, which do not grow at 37 C, and plant-pathogenic *Alternaria* species) are allochthonous, passing through from environmental or dietary exposure without colonizing the gut or exerting any influence on the gut microbiota or host.

We propose that the 10 *Candida* species whose niche is categorized as "Human/mammalian GI tract" (TABLE I)—*Candida albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, *C. lusitaniae*, *C. dubliniensis*, *C. rugosa*, *C. orthopsilosis* and *C. intermedia*—are predominantly gut organisms. Furthermore, based on frequency of detection combined with imperfect/uncertain ITS sequence identification, *Malassezia* species (reported from six, seven and eight studies), *Cladosporium* species (10 studies) and *Galactomyces geotrichum* (seven studies) deserve closer scrutiny as possible gut organisms, as does *Saccharomyces cerevisiae* (19 studies). The ubiquity of *S. cerevisiae* in food and drink may go far toward explaining its abundance; its ability to persist in the gut deserves further study. The only filamentous fungus in this list is *Cladosporium*, whose presence may prove to be attributable solely to environmental abundance. We consider the other fungi reported from the gut as incidental and unlikely to form a lasting part of any gastrointestinal microbial community, on the basis of physiological constraints (many *Penicillium* species do not grow at 37 C; *Wallemia* species are extreme xerophiles and would not grow at the water-activity found in the human body) or known ecological niche (*Ustilago maydis* is an obligate pathogen of maize).

We illustrate (TABLE I, SUPPLEMENTARY TABLE I) the dynamic and variable nature of the mycobiome in

the number of studies identifying a given fungus and conversely the number of fungi identified in a single study. To address the stability of the mycobiome, a study would need to enroll sufficient subjects and obtain a sufficient number of samples from each subject over time to allow statistically significant conclusions to be drawn; to date this has not been done in humans. In the mouse gut fungal populations vary substantially over time and are influenced by the environment, while bacterial populations remain relatively stable (Dollive et al. 2013). There are both more bacterial species and more individual bacteria in the gut than fungi and thus bacterial communities may be more robust (Underhill and Iliev 2014).

It is common for mycobiome papers to report all fungal taxa identified in their studies, frequently drawing attention to first reports of species from the gut. Unfortunately to date few mycologists have turned their attention to the human mycobiome, leading to several common errors in mycobiome studies that would be—not absent but less pronounced—if the research were being conducted by those familiar with the organisms. Misspellings (including of the model organism "*Saccharomyces cerevisiae*", for which we have seen six non-canonical spellings) are common; however, our own experience suggests that these are as likely to occur in review or proof as at the authors' hands. Even with the adoption of "one fungus, one name" in the Melbourne Code (McNeill et al. 2012), fungal nomenclature remains an esoteric study and species are reported as "new" to the gut when in fact they were reported in earlier studies under one or more names.

THE GUT MYCOBIOME IN HEALTHY AND DISEASED STATES

Since Hippocrates first described oral candidiasis in 400 BC, researchers and clinicians have aimed to explore the roles of commensal and pathogenic fungi in human health and disease (Adams 1939). Compared to the vast amount of literature on the benefits of bacteria in the human gut, the beneficial role of gut fungi, if any, remains largely unexplored. No strong evidence exists for a mutualistic or beneficial relationship between the host and the gut mycobiome (Huffnagle and Noverr 2013). The only living fungus studied in detail with any indications of conferring a health benefit is the probiotic yeast *Saccharomyces cerevisiae* var. *boulardii* ("*S. boulardii*") (Zanello et al. 2009). Clinical trials using *S. boulardii* as a therapeutic strategy have shown significant efficacy in treatment and prevention for various types of diarrhea including traveler's diarrhea, antibiotic associated diarrhea and inflammatory bowel disease (Guslandi et al. 2000, 2003; McFarland 2007; Bravo et al. 2008). In addition to the presumed health benefits, it is proposed that probiotic yeasts may positively interact with probiotic bacteria by enhancing their survival and overall display a synergistic effect (Bik et al. 2006, Suharja et al. 2014). Another potential medical application of probiotic yeasts involves their ability to express disease-fighting proteins known as killer toxins, or mycocins, against pathogenic yeasts, such as *Candida* spp. (Weiler et al. 2003).

Yeasts first were detected in the human GI tract in the early 19th century (Langenbeck 1842). In the early 1900s the presence of yeasts in feces was sporadically documented in the medical literature and studies tried to link their presence to gastrointestinal diseases, such as sprue (a digestive disease characterized by malabsorption commonly reported in tropical regions) (Le Dantec 1908, Ashford 1915, Brabander et al. 1957). Years later, just before World War II, isolates from human clinical samples were identified as yeasts of the genus *Monilia*, which later were reclassified into the genus *Candida* (Martin et al. 1937, Langeron and Guerra 1938, Martin and Jones 1940). *Candida* from the intestines of healthy individuals and those with gastrointestinal disturbances became a popular area of research during the mid-20th century. *Candida* was the most commonly isolated yeast from fecal samples, yet its significance and occurrence in stools had yet to be elucidated due to the fact that heavy loads of *Candida* species were collected from healthy humans (Brabander et al. 1957). The history of *Candida* detection in disease states and known ability of *Candida* yeasts to cause infection led physicians in the late 1980s to propose hypotheses linking unhealthy habits to *Candida* overgrowth in the intestine (Truss 1981, Schulze and Sonnenborn 2009). Mycophobia was spreading due to the false interpretation of yeasts isolated from the mouth or stool as fungal infections (Seebacher 1996). The persistence of mycophobic attitudes may be readily observed by anyone performing a web search on "*Candida*".

Characterizing fungal populations (species composition, diversity, relative abundance, alterations in the fungal community) during different disease states may inform knowledge of cause and effect. In the gut higher fungal diversity has been observed in patients with Crohn's disease, hepatitis B and pouchitis than in healthy individuals (Kübacher et al. 2006, Ott et al. 2008, Chen et al. 2011, Li et al. 2014). However, this is not the case for the mycobiome at other diseased body sites. Drawing broad conclusions about fungal diversity, colonization and disease is difficult due to the low number of studies, sample numbers and uncertainty across body sites.

The most common yeasts associated with disease are *Candida*, *Histoplasma*, *Blastomyces* and *Cryptococcus* and

TABLE I. Fungi reported in multiple studies from the gastrointestinal tract of humans

Niche	Fungal taxa
Human/mammalian GI tract	*Candida albicans*[2] (1, 3, 4, 6, 7, 9, 11, 12, 15, 16, 19, 20, 21, 22, 23, 24, 26, 28, 29, 30, 31, 32, 35) (also reported as *Endomyces albicans*[1] [2], *Oidium albicans*[1] (2), *Parasaccharomyces ashfordii*[1] [2])
	Candida tropicalis[2] (1, 3, 4, 5, 6, 7, 13, 16, 20, 21, 22, 23, 31, 32, 34, 35) (also reported as *Monilia candida* Bon.[1] [2])
	Candida parapsilosis[2] (3, 4, 5, 7, 16, 20, 21, 22, 24, 28, 32, 33, 35)
	Candida glabrata[2] (1, 4, 6, 15, 19, 20, 21, 24, 26, 30) (also reported as *Cryptococcus glabratus*[1] [2], *Torulopsis glabrata*[1] [7])
	Candida krusei[1] (1, 3, 4, 6, 7, 17, 20, 24, 32) (also reported as *Mycoderma monosa*[1] [2]), current name: *Candida acidothermophilum*
	Candida lusitaniae[2] (1, 3, 4, 5, 20) (also reported as *Clavispora lusitaniae*[2] [15])
	Candida dubliniensis (15, 22, 23, 26)
	Candida rugosa[2] (16, 17, 20) (also reported as *Mycoderma rugosa*[1] [2])
	Candida orthopsilosis[2] (3, 5)
	Candida intermedia[2] (3, 6)
Human/mammalian associated, elsewhere	*Malassezia globosa*[2] (5, 8, 13, 14, 15, 17, 22, 31)
	Malassezia restricta[2] (5, 13, 14, 15, 16, 17, 31)
	Malassezia pachydermatis[2] (6, 13, 14, 15, 17, 31)
	Candida guilliermondii[1] (1, 3, 7, 20), current name: *Blastodendrion artzii*
	Trichosporon asahii[2] (3, 15, 17)
	Blastoschizomyces capitatus[1] (20) (also reported as *Dipodascus capitatus* [34]), current name: *Geotrichum capitatum*
	Candida zeylanoides[1] (1) (also reported as *Candida krissii* [6])
	Cryptococcus neoformans (22, 23)
	Malassezia sympodialis (16, 31)
	Trichosporon dermatis (5, 26)
Probable foodborne	*Saccharomyces cerevisiae*[2] (1, 3, 5, 6, 8, 14, 15, 16, 17, 19, 21, 22, 23, 24, 25, 26, 28, 31, 34)
	Penicillium allii[1] (13), *P. camemberti*[2] (13), *P. chrysogenum*[2] (15, 23, 26) (= *Penicillium notatum*[1] [7, 34]), *P. commune* (31, 34), *P. dipodomyicola*[1] (13), *P. freii* (6), *P. italicum* (26), *P. solitum* (14)
	Debaryomyces hansenii[2] (5, 8, 15, 16, 31) (also reported as *Candida famata*[1] (1, 19), *D. fabryi* [5])
	Candida sake (16, 34) (also reported as *Candida austromarina* [6, 26])
	Penicillium roqueforti (16, 28, 31, 34)
	Aspergillus niger[2] (7, 16, 31, 33)
	Candida kefyr[1] (1, 4, 19), current name: *Atelosaccharomyces pseudotropicalis*
	Aspergillus flavus[1] (14), *Aspergillus oryzae* (31)
	Saccharomyces bayanus (5, 26)
	Agaricus bisporus (10, 31)
Plant associated	*Cladosporium cladosporioides*[2] (5, 7, 21, 26, 31), *C. bruhnei* (14), *C. herbarum*[1] (32) (= *Davidiella tassiana*[2] [15, 16]), *C. macrocarpum*[1] (33), *C. sphaerospermum*[2] (21, 32, 33), *C. tenuissimum* (21)
	Alternaria alternata (15, 31), *A. brassicicola* (23), *A. tenuissima* (31)
	Sclerotinia sclerotiorum (15, 22, 23, 26)
	Botryotinia fuckeliana (22, 26), current name: *Botrytis cinerea*
	Fusarium graminearum (31), *F. culmorum* (16)
	Fusarium oxysporum (22, 26)
	Fomitopsis pinicola (15, 26)
	Moniliophthora perniciosa (8, 23), current name: *Crinipellis perniciosa*
	Ustilago maydis (8, 26)
Other	*Galactomyces geotrichum*[2] (6, 13, 15, 16, 17, 26, 28)
	Aspergillus sydowii[1] (34), *Aspergillus versicolor*[2] (6, 7, 13, 28, 33)

TABLE I. Continued

Niche	Fungal taxa
	Yarrowia lipolytica[2] (8, 15, 20, 26)
	Aureobasidium pullulans[2] (6, 26, 32)
	Chaetomium globosum (6, 8, 26)
	Geotrichum candidum[2] (17, 20) (also reported as *Galactomyces candidum* [15])
	Aspergillus clavatus (22, 23)
	Aspergillus fumigatus (31, 34)
	Candida colliculosa[1] (3, 4)
	Candida sphaerica[1] (1, 3)
	Candida utilis[1] (1, 3), current name: *Candida guilliermondi* var. *niratophila*
	Cyberlindnera jadinii (31) (also reported as *Pichia jadinii* [16])
	Eurotium rubrum (31) (also reported as *Aspergillus ruber*[1] [14])
	Glomerella sp. (16, 18)
	Kluyveromyces hubeiensis (17, 27)
	Metschnikowia sp. (16, 18)
	Neosartorya fischeri (8, 31)
	Saccharomyces castellii (22, 23), current name: *Naumovia castellii*
	Sclerotium sp. (14, 26)
	Rhodotorula mucilaginosa (15, 26) (also reported as *Rhodotorula pilimanae*[1] [7])
	Cryptococcus tephrensis (16, 31)
	Cystofilobasidium capitatum[2] (14, 26)
	Filobasidium globisporum (15, 26)
	Mrakia sp. (16, 31)
	Rhodotorula glutinis[1] (20) (also reported as *Saccharomyces glutinous*[1] [2])
	Torula rubra[1] (2, 7), current name: *Rhodotorula rubra*
	Wallemia muriae (6, 31)
	Wallemia sebi (6, 10)

Note: No superscript indicates fungi were detected by culture-independent method.

[1] Fungi were detected by culture-dependent method.

[2] Fungi were detected by both culture-dependent and -independent methods.

References: (1) Agirbasli et al. 2005, (2) Anderson 1917, (3) Angebault et al. 2013, (4) Biasoli et al. 2002, (5) Cano et al. 2014, (6) Chen et al. 2011, (7) Cohen et al. 1969, (8) David et al. 2014, (9) DiGiulio et al. 2008, (10) Dollive et al. 2012, (11) Finegold et al. 1974, (12) Finegold et al. 1977, (13) Gouba et al. 2013, (14) Gouba et al. 2014a, (15) Gouba et al. 2014b, (16) Hallen-Adams et al. 2015, (17) Hamad et al. 2012, (18) Hoffmann et al. 2013, (19) Jobst and Kraft 2006, (20) Khatib et al. 2001, (21) LaTuga et al. 2011, (22) Li et al. 2012, (23) Li et al. 2014, (24) Macura and Witalis 2010, (25) Nam et al. 2008, (26) Ott et al. 2008, (27) Pandey et al. 2012, (28) Scanlan and Marchesi 2008, (29) Soyucen et al. 2014, (30) Stewart et al. 2013, (31) Suhr 2015, (32) Taylor et al. 1973, (33) Taylor et al. 1985, (34) Ukhanova et al. 2014, (35) von Rosenvinge et al. 2013.

to a lesser extent species of *Geotrichum*, *Malassezia*, *Pichia*, *Rhodotorula*, *Saccharomyces* and *Trichosporon*. With the exception of *Blastomyces*, each of these fungal genera has been reported in the GI tract; however, with the exception of *Candida*, and *Saccharomyces* in immunocompromised patients, yeasts in the gut are not implicated in disease. The most common filamentous fungi associated with disease and found in the gut are *Aspergillus* species. While best known for causing lung infections, gut aspergillosis is reported in patients with blood malignancies (Kazan et al. 2011, Li et al. 2014). Other filamentous fungi found in the gut and causing infections include *Alternaria*, *Scedosporium*, *Paecilomyces* and *Trichoderma*; infections with these species are much less common than with *Aspergillus*. In addition to involvement of specific fungi (notably *Candida* species) in disease, an overall increase of gut fungal diversity and/or abundance has been associated with inflammatory bowel diseases, hepatitis B, pouchitis and gastric ulcers (TABLE II and references cited therein).

Candida species are normal, harmless commensals on many human body sites and have been consistently reported in gut fungi studies. *Candida* species resident

TABLE II. Changes in the gut mycobiota associated with disease

Disease status	Sample type and size	Methodology	Primers	Findings	Reference
Type 1 diabetes	Feces, n = 35	Culture	n/a	*C. albicans* identified in 40% of subjects, significant difference from 35 controls	Soyucen et al. 2014
Inflammatory bowel disease	Colonic biopsies, Crohn's disease n = 31 Ulcerative colitis n = 26	18S rDNA, DGGE, clone libraries	NS0/EF3 NS1/FR1 BF2/TR1-RP	Higher mean fungal diversity in patients with CD; significant difference from 47 controls	Ott et al. 2008
Crohn's disease	Ileal mucosa and feces, n = 19	18S rRNA, DGGE, cloning	NS1/FR1, EF390/GC-FR1	Fungal richness and diversity significantly increased in patients; *C. albicans* and *C. tropicalis* abundant in patients and absent in seven controls	Li et al. 2014
Familial Crohn's disease	Feces and mouth swabs; n = 129 CD patients n = 113 healthy relatives	Culture, biochemical tests, latex agglutination	n/a	*C. albicans* significantly more frequent in CD patients and their healthy relatives than from 14 control families	Standaert-Vitse et al. 2009
Preterm infants (<32 wk)	Feces, n = 32, (seven NEC, 13 sepsis)	28S rDNA, DGGE, cloning	U1/U2-GC	Fungal colonization in half of infants; no fungal species were observed in infants who developed NEC	Stewart et al. 2013
Intestinal transplant	Ileal effluent and feces; n = 2	18S rDNA, DGGE, cloning	NS1/FR1 EF390/GC-FR1	High fungal diversity soon after transplant; less diversity >16–20 wk post transplant	Li et al. 2012
Hepatitis B	Feces, hepatitis B cirrhosis n = 38, chronic hepatitis B n = 35	Culture 18S, clone libraries, RFLP	Unspecified	Diversity of enteric fungi positively correlated with disease progression	Chen et al. 2011
Hematologic malignancy or disorder	Feces, n = 80	Culture, germ tube test, biochemical test	n/a	Non-*albicans Candida* spp. significantly higher in patients; *C. glabrata* more prevalent in patients than 61 controls	Agirbasli et al. 2005
Hospital inpatients	Feces, n = 34	Culture, germ tube test, biochemical test	n/a	Inpatients higher prevalence of yeasts; *C. glabrata* more prevalent in inpatients	Khatib et al. 2001
Extremely low birth weight infants	Feces, n = 11	ITS, 454 pyrosequencing, metagenomic shotgun sequencing	ITS3/ITS4	*Candida* spp. and *Clavispora* sp. dominated; *Candida quercitrusa* most abundant	LaTuga et al. 2011

TABLE II. Continued

Disease status	Sample type and size	Methodology	Primers	Findings	Reference
Diabetes	Feces, type 1 n = 27, type 2 = 17	18S, quantitative real-time PCR	Unspecified	*Candida* spp. significantly greater in T1 and T2 patients than 17 controls	Gosiewski et al. 2014
Graft vs. host disease	Feces and oral sample, GVHD n = 59 GI-GVHD n = 37	Culture	n/a	Patients colonized with *Candida* spp. had a significantly higher rate of grade II–IV acute GVHD	van der Velden et al. 2013
Pouchitis	Biopsy and feces; n = 36	18S, DGGE, cloning	NS1/FR1-GC	Patients who develop pouchitis have higher fungal diversity and lower bacterial diversity	Kübacher et al. 2006
Varying symptoms and complaints	Feces; n = 308	Culture, biochemical tests, latex agglutination	n/a	Smoking habits highly associated with *Candida* colonization, also associated with *Candida*-vaginitis and allergies	Jobst and Kraft 2006
Gastric ulcers	Gastric juice, n = 293	Culture, biochemical test	n/a	Significant fungal colonization $>10^4$ CFU/mL in patients with gastric ulcers	Zwolińska-Wcisło et al. 2006

in the GI tract are considered a major reservoir and source of infections such as invasive candidiasis (Nucci and Anaissie 2001). *C. albicans*, the predominant gut fungus, colonizes the GI tract but has the ability to invade tissues and disseminate in the body when the gut microbiome is disrupted, intestinal mucosal permeability is increased or the host is immune-suppressed. *Candida* gut overgrowth has been associated with a number of diseases such as diabetes, hematologic malignancies, Crohn's disease and graft vs. host disease and populations such as hospital inpatients and extremely low birth weight infants (TABLE II). Patients with gastrointestinal disorders such as ulcerative colitis and Crohn's disease are more frequently and heavily colonized by *C. albicans* than are control groups (Ksiadzyna et al. 2009, Standaert-Vitse et al. 2009).

Malassezia is commonly reported in fecal samples (Chen et al. 2011, Hamad et al. 2012, Li et al. 2012, Gouba et al. 2013, Suhr 2015). *Malassezia* species are the dominant fungi on the skin surfaces of mammals, where they are dependent on the host for lipids and are associated with various superficial skin diseases and dandruff (Gupta et al. 2004) and may become associated with feces through skin contact during defecation. Conversely the availability of lipids in the GI tract, particularly the small intestine, could select for gut colonizing *Malassezia* species.

Aspergillus species have a worldwide distribution and their ubiquity in the environment exposes humans to *Aspergillus* spores daily. Invasive aspergillosis has increased significantly in recent decades and is the most common filamentous fungal lung infection in immunocompromised patients (Groll et al. 1996, McNeil et al. 2001), while noninvasive colonization of the nasal cavities and lungs is common in immunocompetent persons (Giri et al. 2013). *Aspergillus fumigatus* is the most prevalent species of the 200 aspergilli described and is the main cause of human infections (Dagenais and Keller 2009); *A. flavus, A. glaucus, A. niger, A. nidulans, A. parasiticus* and *A. terreus* also are commonly associated with aspergillosis (Moore et al. 2011). Numerous species of *Aspergillus* have been reported in the GI tract of humans (TABLE I), some likely due to transit from the airways (Beck et al. 2012). *Aspergillus* species clearly possess the ability to survive in and colonize the human body; however, species detected in the gut also are common in the environment and/or colonizing food, and their presence in the gut is likely a reflection of general abundance rather than of persistent colonization.

MYCOBIOME AND HOST IMMUNITY

The GI tract is home to the majority of both the human body's commensal microorganisms and

immune cells. Little is known about the interaction between commensal intestinal fungi and the host immune system. Several players of the immune system have been reported to have critical roles in fungal recognition and host defense against disseminated fungal infections. These include Dectin-1, IL-17 and IL-22 (Iliev and Underhill 2013). Dectin-1 is a C-type lectin that plays a role in the innate immune response by functioning as a pattern-recognition receptor and recognizing beta-glucans found in the cell walls of fungi. In mice Dectin-1 is of critical importance to defend against pathogenic fungi such as *Pneumocystis carinii* and *C. albicans* (Saijo et al. 2007, Taylor et al. 2007). Humans deficient in Dectin-1 suffer recurrent mucocutaneous candidiasis infections (Ferwerda et al. 2009). Genetic polymorphisms of Dectin-1 also have been associated with increased severity of ulcerative colitis (Iliev et al. 2012, Underhill and Iliev 2014).

Cytokines IL-17 and IL-22 have been implicated in mucosal and antifungal immunity. Mice deficient in components of the IL-17 pathway have increased susceptibility to oral candidiasis and skin infections (Conti et al. 2009, Kagami et al. 2010). Furthermore, IL-22 serves as a first line of defense against candidiasis in mice because IL-22-deficient mice are more susceptible to GI candidiasis (de Luca et al. 2010). Mucosal immune responses to fungi are different across human body sites. A complete understanding of the interaction between commensal fungi and the immune system has yet to be unveiled.

DIET AND THE GASTROINTESTINAL MYCOBIOME

Diet is a known environmental factor that influences the structure and diversity of microorganisms in the gut. Resident bacterial populations are shown to be associated with diet and long-term dietary patterns (David et al. 2014). However, few studies have investigated the relationship between diet and the human intestinal mycobiome. One recent human study demonstrated that consumption of high amounts of carbohydrates was positively associated with *Candida* spp. colonization, while a diet high in amino acids, fatty acids and protein was negatively associated with *Candida* spp. (Hoffmann et al. 2013). Fungal abundance in the gastrointestinal tract also was associated strongly with the composition of short-term diet. Diets with meat significantly increase *Penicillium* spp. (David et al. 2014), while Ukhanova et al. (2014) showed a decrease in *Candida* and *Penicillium* species following pistachio and almond consumption. Unsurprisingly fungi consumed as part of the diet (edible mushrooms, yeasts and *Penicillium* spp. involved in cheese making) can be detected in fecal samples (David et al. 2014, Suhr 2015).

Intestinal populations of microorganisms are suspected of contributing to obesity by way of diet (Ley et al. 2006). The role of gut fungi in obesity is unknown. Only one study has addressed this, focusing on the fungal communities in the human gut of a single obese person and detecting 18 fungal species (Gouba et al. 2013.). Conversely a study identifying the fungal community of a single anorexic human reported a "restricted" diversity of 10 fungal species (Gouba et al. 2014a). However, neither of these numbers seem exceptional; other gut fungi studies report 0–24 fungal taxa in healthy individuals (Hallen-Adams et al. 2015, Suhr 2015).

CROSS-KINGDOM INTERACTIONS

Interactions among microorganisms within the GI tract have long been recognized as important determinants of community function (Savage 1977). Inhabitants are unlikely to act in isolation in the gut and therefore live in complex associations with one another. Residents of the gastrointestinal microbiota are constantly interacting with one another, competing for nutrients and space and producing compounds that directly inhibit growth or kill potential competitors (Little et al. 2008). Microbes in the gut also may form mutualistic and/or commensal interactions with one another cooperating via syntrophy, using metabolic waste products of another organism as nutrients, and constructing interspecies antibiotic-resistant biofilms (Rodríguez-Martínez and Pascual 2006, Woyke et al. 2006). Hoffman et al. (2013) has best described the correlations between fungi-bacteria and fungi-archaea. *Candida* and *Saccharomyces* commonly co-occur with bacterial taxa *Faecalibacterium*, *Bacteroides*, Lachnospiraceae and Ruminococcaceae, and these fungal genera are also positively associated with the archaeon *Methanobrevibacter* and negatively associated with the archaeon *Nitrososphaera*. Further analysis showed that *Candida* was negatively associated with *Bacteroides*. Hallen-Adams and colleagues (2015) observed a negative correlation between *Escherichia/Shigella* and the fungi *Malassezia* and *Trichosporon*, and the presence of *Candida tropicalis* was positively associated with *Bacteroides* and negatively associated with *Eubacterium*.

Bacteria and fungi indisputably interact physically and chemically with one another within an ecosystem (Peleg et al. 2010). These interactions influence overall survival, colonization and virulence. Perhaps the most important bacterial-fungal interaction led to the discovery of penicillin (Fleming 1929). Physical interactions between fungi and bacteria include forming mixed biofilms with one another and the ability of bacteria to attach to fungal hyphae, inhibiting filamentation and biofilm formation (Adam et al. 2002, Peleg

et al. 2008). Bacteria also produce antifungal molecules that affect morphology and virulence of *Candida* (Hogan et al. 2004). Bacteria have the ability to modify the environment by lowering the pH and preventing hyphae formation by *C. albicans* (Buffo et al. 1984).

Bacteria and fungi are known to inhabit and interact with one another at multiple human body sites. The species composition of the two may become beneficial or detrimental to the human host. Within the gastrointestinal microbiota, colonization resistance is a known interaction that prevents overgrowth by endogenous organisms. The bacterial microbiota reduces *C. albicans* colonization by excluding and out-competing *Candida* for adhesion sites and producing inhibitory molecules (Kennedy and Volz 1985). Controlling fungal colonization, especially by opportunists, with the use of probiotic bacteria is appealing. One study showed the probiotic bacteria *Lactobacillus acidophilus* and *Lactobacillus casei* induce protection against systemic candidiasis in mice (Wagner et al. 2000). Short-chain fatty acids (butyric acid) produced by lactic acid bacteria also inhibit filamentation and may prevent *C. albicans* from causing disease in the gut (Noverr and Huffnagle 2004a).

When broad-spectrum antibiotics are administered, these have the potential to cause serious disruption to the entire bacterial community in the GI tract, perturb the equilibrium and allow the host to become susceptible to infections by normally benign, commensal fungi such as *C. albicans* (Samonis et al. 1993). Antibiotics are, therefore, a major risk factor for candidemia in hospitalized patients (Wey et al. 1989, Nucci and Colombo 2002, Zaoutis et al. 2010). Conversely post-antibiotic recolonization of the bacterial gut microbiota is shaped and altered by the presence of *Candida*. In the stomach of microbiome-disturbed mice *C. albicans* prevents *Lactobacillus* regrowth after antibiotic treatment and promotes colonization of *Enterococcus* (Mason et al. 2012a). Presence of *C. albicans* in the murine cecum after antibiotic treatment promotes Bacteroidetes populations, *Enterococcus faecalis* persistence, and inhibits *Lactobacillus johnsonii* (Mason et al. 2012b). Another recent study demonstrated that the exogenous addition of *C. albicans* during treatment with the cefoperazone in mice led to yeast overgrowth and substantially altered reassembly of the bacterial community after treatment (Erb Downward et al. 2013).

CONCLUSION AND FUTURE DIRECTIONS

Study of the gastrointestinal mycobiome is still in its infancy. Given the few species consistently reported in gut mycobiome studies (*Candida* spp. and other Saccharomycetalean yeasts, common environmental molds such as *Aspergillus, Cladosporium* and *Penicillium*) and the low abundance of fungi in the gut, it is unlikely that fungi will be found to play as broad and diverse a set of roles as gastrointestinal bacteria in host fitness and well-being. The final word on gut fungal diversity is yet to come; gut-fungal studies span nearly a century (albeit with a >50 y gap, 1917–1969), yet species new to the gut are reported in nearly every study. Some of this diversity is illusory, and much represents environmental and foodborne organisms that do not contribute to gut ecology.

There remains much to learn and worth learning about the mycobiota: the role of *Candida* species in a healthy microbiome, for instance, the effect of diet on mycobiota and the stability of the mycobiome over time all require much larger and broader studies than have been undertaken to satisfactorily address. Well-designed studies, incorporating environmental sampling and dietary data, are needed to determine the role, if any, of environmental molds. A reliance on BLAST-query results for identification may underrepresent as well as overrepresent diversity; in many cases the closest BLAST hit does not allow species identification, and active members of the gut community remain undescribed (e.g. *Malassezia* spp. and yeasts in the Dipodascaceae; Hallen-Adams et al. 2015).

Metagenomic characterization of the gut mycobiome is already possible in a targeted fashion for organisms with sequenced genomes. Areas of interest include many questions about *Candida* basic biology (Is mating occurring? How do various conditions [diet, microbial composition, host health and fitness] influence the expression of virulence factors?) and questions about nutrition—whether gut-adapted *Malassezia* are accessing and using lipids from the host's diet (or directly from the host) and whether any gut fungi are generating host-usable carbohydrates from dietary fiber, as is well-documented in insects (Nguyen et al. 2006) and herbivorous mammals (Trinci et al. 1994).

The use of model systems, such as mice with limited, defined microbiomes (gnotobiotic), remains underutilized for fungi, although mouse models are a mainstay for bacterial microbiome studies. Mice do not naturally harbor *Candida* species and require some repression of the natural microbiome to sustain *Candida* colonization (Koh 2013), while the "natural" gut mycobiome of laboratory mice is strongly influenced by the environment (food source, bedding etc.; Hallen-Adams pers obs). Mouse studies to date deal primarily with *Candida* and with disease (either candidiasis or the role of *Candida* in other diseases such as colitis (e.g. Jawhara and Poulain 2007, Szabo and MacCallum 2011), but the potential exists to gain a real understanding of fungal interactions, both with other

microbes and with the host. As we forge ahead into this exciting era it is hoped that mycologists will lead the way to a better understanding of the role of fungi in the human gut and throughout the body.

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