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Mycobiome: An emerging perspective in fungal biology!

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ABSTRACT

Fungi represent an important and highly diverse group of eukaryotic microbes on earth. They play a vital role in ecosystem by driving biogeochemical cycling and nutrient uptake eventually influencing the ecological fitness. As compared to bacterial counterpart of microbiome the knowledge about fungi is still lacking from a mycobiome perspective which represents the total fungal biota in the environment. Fungi are widely distributed across all major biomes on earth. However, global fungal diversity patterns are determined by abiotic factors, geographical location, climate change and other environmental factors. With advances in high throughput sequencing platforms fungal biodiversity has been unraveled at a greater depth. This has shed light on fungal community dynamics and its contrasting features from microbiome perspectives. Additionally, a growing body of evidence suggests inter and intra-kingdom interactions and possible role of mycobiome as an integral part of the human welfare. In this article, the mycobiome is discussed in context of its association and significance in major biomes of earth.

Keywords: Fungi, biomes, next generation sequencing, mycobiome, microbiome

INTRODUCTION

This is the period of discovery when researchers are focusing upon enumeration of global microbial diversity placing it around 1 trillion (10^{12}) inhabiting the earth (Locey and Lennon, 2016). At the same time significance of such findings in understanding the role of microbial communities in ecosystem functioning is also expanding. The huge number of microbial communities present on earth sets a challenge to find links between diversity and function.

Microbial diversity on earth includes bacteria, archaea, viruses and eukaryotic microbes which together compose a microbiome although this term is synonymously being used largely for bacteria. Therefore, the term mycobiome coined by Ghannoum *et al.* (2010) is used to represent the underrepresented component of microbiome, the fungus. Despite ubiquitous presence of bacteria and fungi in all ecosystems, domain bacteria predominate more than fungi in abundance (5.1 million species; Blackwell, 2011) and the amount of total DNA (~1.7×10^{27} Mb; Landenmark *et al.*, 2015) in the biosphere. Relative to mycobiome, patterns and processes in understanding microbiome are better documented (Dietert and Dietert, 2015) not only in humans but also in plant system (Berendsen *et al.*, 2012) and other biomes. However, many researchers are currently exploring fungi which have been largely ignored as an integral part of microbiome (Cui *et al.*, 2013). Fungi are widely distributed across all ecosystems as single celled or mycelial form, dominating more so under stressful conditions; they also show hyphal lifestyle wherein they are mainly involved in decomposition processes (**Fig. 1**). Mycobiome includes microscopic forms as well as world's largest and oldest organism, *Armillaria solidipes* (previously known as *Armillaria ostoyae*). This humongous fungus encompasses an area 3.7 sq miles (9.6 sq km) and is considered to be 1,900 to 8,650 year old (Ferguson *et al.*, 2003). Fungi possess unique physiological, morphological characteristics and ecosystem function therefore it becomes reasonable to study how these organisms contribute to ecosystem dynamics.

Our current knowledge in characterizing mycobiome has improved by the development of next generation sequencing

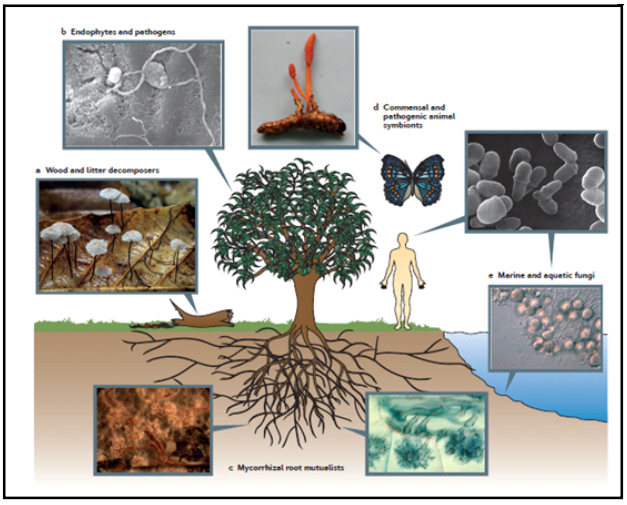

Fig 1: Functional diversity of the mycobiome in nature. Reprinted by permission from Macmillan Publishers Ltd: (*Nature Reviews Microbiology*) (Paey *et al.*, 2016), copyright (June, 2016).

(NGS). Furthermore, use of modern bioinformatics tool has helped in discovering novel lineages thereby reshaping the tree of life (Hug *et al.*, 2016). Growing interest in studying mycobiome is supported by several reasons. First, as the role of fungi towards ecosystem processes, driving nutrient cycling and as causative agent in many infectious diseases is extensively studied (Treseder and Lennon, 2015) which has further evoked the curiosity to investigate the functions encoded by the microbial genes and how they largely influence the overall health of the host (Qin *et al.*, 2010). Secondly, growing evidence for significant role of fungus in host fitness and disease progression leads to investigate abiotic factors which shape distinct mycobiome (**Fig. 2**). Also, knowledge of mycobiome becomes essential in making deeper understanding of how microbiome affects ecosystem processes (Oever and Netea, 2014).

In this review we present a brief overview of our present knowledge on the diversity of fungi in major earth biomes

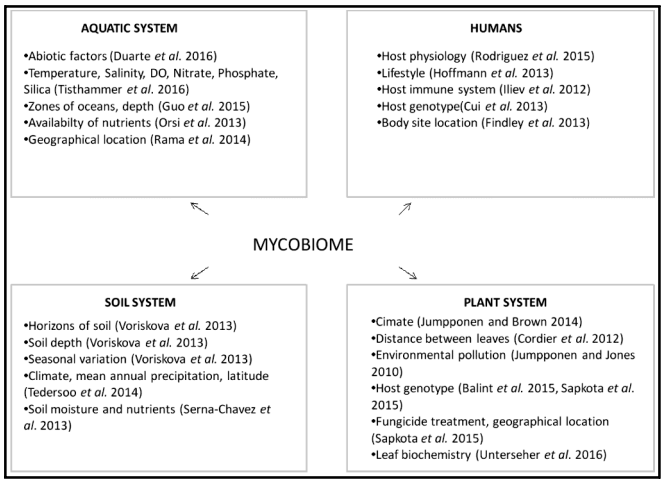

Fig 2: Factors affecting mycobiome composition in various ecosystems

with a focus on how their communities shift with slight perturbation, thus, suggesting outlook to improve our understanding on the role of mycobiome in regulating ecosystem processes.

DIVERSITY AND ABUNDANCE OF FUNGI IN MAJOR BIOMES

I. Human System

The magnitude with which fungi colonize different body sites is much smaller than bacteria (Underhill and Iliev, 2014). The composition of mycobiome varies between the different body sites and thus is believed to play an important role in the state of both health and disease. Since they are a minor part in microbiome, it faces many challenges such as lower abundance constituting 0.1-1 % of total microbiome and second isolation of fungal DNA may be difficult (Qin *et al.*, 2010; Huffnagle and Noverr, 2013). As reported even ancient oral microbiome is dominated by 99.3% bacteria and only less than 0.005 % fungi are present due to relatively low proportion of fungal DNA being conserved (Warinner *et al.* 2014).

(a) Gut mycobiome: The human microbiome in our body is of the same order (updated revised ratio 1:1; Sender *et al.* 2016). Human gut contains 66 genera and 184 species of fungi (Underhill and Iliev, 2014). Hoffmann *et al.* (2013) have identified *Saccharomyces* (89%), *Candida* (57%) and *Cladosporium* (42%) in fecal samples from 98 healthy individuals as most prevalent genera in human gut. However, more research is required to establish that certain genera are exclusively found in gut or are influenced by dietary intake.

Dysbiosis of gut fungal mycobiota is associated with various diseases like increased diversity and abundance of *Candida* sp., *Gibberella moniliformis, Alternaria brassicicola* and *Cryptoccocus neoformans*. These appear at the site of inflamed mucosa with decreased presence of *Saccharomyces cerevisiae* in the fecal mycobiome of patients with Crohn's disease (Li *et al.*, 2014). Similar results have been reported in pediatric patients with IBD and healthy controls (Chehoud *et al.*, 2015). During IBD, pathogenic fungi, *Candida* and *Trichosporon* are highly abundant with decrease in non-pathogenic genus *Sacccharomyces* (Iliev *et al.* 2012). Now more common diseases such as obesity are found to be influenced by mycobiome. For instance, obese people have increased abundance of fungi belonging to the phylum *Ascomycota*, classes *Saccharomycetes* and *Tremellomycetes*, and families *Dipodascaceae* and *Saccharomycetaceae* compared with non-obese subjects (Rodriguez *et al.*, 2015).

(b) Oral mycobiome: According to Human Microbiome Project Consortium (HMPC), human mouth is heavily colonized by microbes and in complexity it is second to only colon. Around 50 - 100 bacterial genera have been identified in healthy human subjects (Bik *et al.*, 2010). The first time oral mycobiome of 20 healthy human subjects was characterized through deep sequencing using ITS sequence (Ghannoum *et al.*, 2010) that showed the presence of 85 fungal genera. Among ~15 most prevalent genera, pathogens such as *Aspergillus*, *Cryptococcus, Fusarium* and *Alternaria* were found as a part of resident mycobiome which varied greatly between different individuals. Beside ~15 most prevalent fungal genera, *Malassezia* and *Epicoccum* were found as additional fungal forms (Dupuy *et al.*, 2014). Significant link has been established between oral mycobiome and HIV infected individuals where *Candida*, *Aspergillus* and *Fusarium* are most abundant fungal genera; no such pattern changes were observed in the microbiome (Mukherjee *et al.,* 2014). The functional aspect of wide diversity in oral mycobiome and high variability within species could be essential to manage environmental stress.

(c) Lung mycobiome: Investigators are now looking at other body sites for fungal communities like lung which was previously thought to be a sterile organ. Charlson *et al*. (2012) reported presence of *Davidiellaceae*, *Cladosporium, Eurotium, Penicillium* groups in healthy control. *Candida*, *Neosartorya*, *Malassezia*, *Hyphodontia*, *Kluyveromyces* are most prevalent genera in diseased condition like cystic fibrosis (Delhaes *et al.*, 2012). Exclusive dominance of *Candida* is also reported in lung transplant patients (Charlson *et al.*, 2012) which is most likely due to immuno-compromised condition and long term antibiotic use. Respiratory tract and oral cavity are exposed to environmental pathogens like *Aspergillus* which is commonly found in healthy lung and shares other genera of oral mycobiome (Ghannoum, *et al.*, 2010). In immuno-compromised condition commensal forms may turn into pathogen causing aspergillosis (Underhill and Iliev, 2014)

(d) Skin mycobiome: *Malassezia, Rhodotorula, Debaromyces, Cryptococcus* and *Candida* are common skin commensal fungal genera identified based on culture based approach (Roth and James, 1988). With use of high throughput sequencing, Findley and colleagues (2013) have characterized healthy skin mycobiome wherein genus *Malassezia* dominated 11 torso and arm sites and plantar heel, toenail and toe web. Mycobiome is altered in dandruff afflicted scalps and has been reported to be dominated by *Acremonium, Filobasidium, Penicillium,* uncultured soil fungus*, Malassezia, Cryptococcus, Didymella, Rhodotorula, Eupenicillium, Coniochaeta* and an uncultured Ascomycete (Park *et al*., 2012). *Malassezia* is generally most common

form in healthy and diseased state and is ecologically hyper-diverse fungus on earth (Amend, 2014).

II. Aquatic System

Fungi in marine ecosystem are both non-diverse and low in abundance as compared to fungal isolates found in terrestrial or other environments (Peay *et al*., 2016). This could be related to the fact that very low fraction (0.6%) of documented fungi are derived from marine environment. Several reports show the dominance of Ascomycetous and Basidiomycetous forms in deep marine sediments, hydrothermal vents, mangroves, corals and anoxic marine waters (Bass *et al*., 2007, Simoes *et al*., 2015, Amend *et al*., 2012). Yeasts and some unknown fungal forms are dominant in these environmental conditions (Le Calvez *et al*., 2009; Tisthammer *et al*., 2016). Phylogenetic analysis based on unique fungal SSU rDNA sequences analyzed *Neurospora, Aspergillus, Cordyceps, Fusarium, Ustilago* like lineages, *Coprinus, Antrodia* and *Exidia* which were found to be more diverse in marine habitats (Richards *et al*., 2012). For the first time members of *Chytridiomycota* was reported by Le Calvez and colleagues (2009) in deep vent ecosystem. They used SSU rRNA to determine fungal diversity in two deep sea hydrothermal vents. Out of 20 different phylotypes, nine were unsuspected phylotypes in vent ecosystem and five were new at genus level, two from *Chytridiomycota* and three from *Basidiomycota*. The species matching 97.7% similarity was found to be a pathogenic fungus, *Chytridium polysiphoniae*. However, diversity of fungi was high in deep sea hydrothermal vents as compared to surface water samples (Massana and Pedr'os Ali'o, 2008). Freshwater ecosystems show presence of members of *Cryptomycota* which plays a significant role in the microbial loop of freshwater ecosystem (Jones *et al.*, 2011).

Edgcomb *et al.* (2011) reported high frequency of Basidiomycete yeast resembling closely *Malassezia* and *Cryptococcus* by targeting both RNA and DNA based diversity profiles. Especially, *Malassezia* a diverse and important group in marine environment (Amend, 2014; Gao *et al*., 2008) shows that marine taxa are interlinked with human and terrestrial genera and do not form a single monophyletic clade. Fungi from marine and terrestrial habitats are capable of making transition to deep sea where they can withstand deep saline conditions due to their membrane composition and structure.

In contrast to a study by Tisthammer *et al.* (2016) distinct mycobiome was observed between sediments and water column where *Ascomycota* and *Basidiomycota* were most abundant datasets whereas *Chytridiomycota* and *Cryptomycota* were present infrequently; only 15.4% of OTUs were shared between water column and sediment samples.

Mangrove fungi are second largest group dominated by *Ascomycota* (76% - 85%) and *Basidiomycota* (14% - 24%) in the rhizosphere sediments. In *Avicennia marina* (gray mangrove), fungal genera *Aspergillus*, *Schizosaccharomyces*, and *Gibberella* dominate the rhizospheric region; also, the rhizosphere harboured distinct mycobiome as compared to bulk soil (Simoes *et al*., 2015).

Fungi are also associated with corals and believed to be mutualistic, commensal to opportunistic pathogen depending upon environment and overall coral health. Metabolically active and diverse resident marine fungal community is dominated by *Basidiomycetes* and *Ascomycetes* in this environment. *Sordariomycetes* and *Dothideomycetes* (*Ascomycota*), and *Agaricomycetes* and *Ustilaginomycetes* (*Basidiomycota*) are the most species rich groups. *Symbiodinium* genotype and water temperature had no discernible impact on the fungal community (Amend *et al.*, 2012). However, much more work needs to be done to unravel functional and nutritive relationship between fungi and coral hosts.

III. Plant System

Microbial communities associated with plants help in nutrient acquisition, growth and increased stress tolerance. Microbe-plant interaction occurs in three regions of plants, viz., rhizosphere, phyllosphere and endosphere. A single tree individual may host as many as 200 species of fungi (Bahram *et al.*, 2010). Rhizosphere microbiome has gained considerable attention and this information has been recently reviewed (Berendsen *et al.*, 2012). A study by Bai *et al.* (2015) analyzed the fungal community using 454 pyrosequencing targeting ITS region and reported presence of *Ascomycota* and *Basidiomycota* as a dominant phylum in the soil sample. *Thelebolus* and *Mortierellales* increased abundantly in the rhizospheric soil as a result of continuous cropping of soybean. *Thanatephorus, Fusarium* and *Alternaria* were predominant fungal pathogens. Another study by Ambardar *et al.* (2016) for the first time reported the dynamics of major fungal phyla in the rhizosphere of *Crocus sativus* and among these the members of phylum *Zygomycota* were most dominant. An interesting fact about microbial dynamics depicted in this investigation was that the cormosphere in flowering and dormant stage was dominated by *Basidiomycota* and *Zygomycota*, respectively clearly implying that fungal diversity is niche and growth stage specific.

The phyllosphere, the habitat provided by the leaves of living plants, is one of the largest microbial habitats on Earth, with an estimated global surface area of more than 4×10^8 km^2 (Morris and Kinkel, 2002). It is mainly colonized by phylum *Ascomycota* followed by *Basidiomycota* (Eusemann *et al.*, 2016). Genotype of plant is a major factor in shaping the mycobiome in phyllosphere than does the geographical distance (Cordier *et al.*, 2012).

IV. Soil System

Soil is a reservoir of thousands of fungal and bacterial species that play an important role in natural and managed agricultural soils (Tardy *et al*., 2015). Fungi are widely distributed in all terrestrial environments and previously detailed understanding of major groups of fungi, the extent of diversity in unique habitats in India, are well documented (Manoharachary *et al.*, 2005). Saprotrophic taxa are more abundant in surface of the forest floor whereas mycorrhizal fungi predominate at soil depth where they show symbiotic association with roots of plants (Lindahl *et al.*, 2007). Unlike

other soil fungi which are not influenced by plant-soil feedbacks, ectomycorrhizal fungi are positively related with host plant and high soil pH. Both groups are actively involved in major function of decomposition therefore variation in their community structure affects the ecosystem processes eventually changing plant productivity and diversity. A comprehensive study of 365 global soil samples from natural ecosystem using pyrosequencing revealed presence of *Basidiomycota* (55.7%), *Ascomycota* (31.3 %), *Mortierellomycotina* (6.3 %) and *Mucoromycotina* (4.4 %) (Tedersoo *et al.*, 2014).

A culture-independent survey of the soil mycobiome in 600 soil samples found 20 most abundant families; predominant families were *Atheliaceae*, *Corticiaceae*, *Cortinariaceae*, *Inocybaceae*, and *Russulaceae*. Like animal and plant system, soil fungi exhibited geographic endemism (Talbot *et al.*, 2014). Fungal communities were found to be divergent but functionally redundant across different biogeographical regions. It is likely due to the involvement of fungi in decomposition process of organic matter. Most importantly a vertical stratification of fungal diversity exists in soil (Lindahl *et al.*, 2007; Voriskova *et al.*, 2013). The diversity in L horizon is influenced more by season than those present in the deeper horizon. In L horizon dominant fungal genera are *Mycena*, *Sistotrema* and *Cryptococcus* while in H and Ah horizon *Russula* and *Lactarius* are present. Abundance of fungal community declines with depth owing to the properties of soil i.e., organic matter content and pH (Voriskova *et al.*, 2013).

ROLE OF METAGENOMICS AND NEXT GENERATION SEQUENCING

Traditional approaches to cultivate fungi in agar medium and classifying based on morphological features cannot predict complete diversity in natural environment. Undoubtedly, advances in sequencing methods have revolutionized our understanding of fungal diversity. Unculturable fungi constitute a major proportion of species like unculturable bacteria which go undetected through traditional methods. It could be best exemplified by the study of Delhaes *et al.* (2012) who found that around 60 % of fungi remain undetected through culture based methods. Out of 247 species found in the digestive tract, only 59 were identified by *in vitro* culture and 207 by molecular techniques (Gouba and Drancount, 2015). With the advent of metagenomics and NGS platforms a great deal about fungal diversity even in unexplored ecosystem like marine and animal is now known with greater resolution (Chen *et al.*, 2011; **Table 1**).

Metagenomics is a shotgun sequencing based method widely adapted to sequence DNA isolated from the environment and draft genomes are reconstructed from genome fragments (Dick *et al.*, 2009). Through this technique organisms can be classified using phylogenetic information and metabolic capability. Besides being a powerful sequencing technique certain drawbacks associated with metagenomics study are the expenses involved and computational challenges (Morgan and Huttenhower, 2012). Furthermore, a major problem associated in assessing fungal diversity is that they constitute a minor component in microbiome samples.

Table 1: Reported diversity of fungi in different biomes

S. No.	Sample and specimen type	Sequencing used, sample size, health status	Dominant fungal composition	Reference
1	Gut mycobiome, fecal samples	Pyrosequencing 454 n= 69, Healthy individuals	*Candida tropicalis*, *Geotrichum gigas*, *Candida sake*, *Cladosporium* sp., *Pichia jadinii*, *Candida albicans*, *Debaryomyces hansenii*, *Candida rugusa*, *Galactomyces geotrichum*, *Malassezia restricta*, *Candida* sp. *GJ13M01*, *Metschnikowia* sp., *Ramularia* sp., *Aspergillus niger*	Hallen-Adams *et al.* (2015)
2	Oral mycobiome, oral rinse samples	Pyrosequencing 454 n= 20 Healthy individuals	*Candida*, *Cladosporium*, *Aspergillus*, *Fusarium*, *Glomus*, *Penicillium*, *Alternaria*, *Saccharomycetales*, *Cryptococcus*, *Ophlosoma*, *Phoma*, *Schizosaccharomyces*, *Zygosaccharomyces*	Ghannoum *et al.* (2010)
3	Skin mycobiome, scalp swabs	Pyrosequencing 454 n=7 Dandruff afflicted scalps	*Acremonium*, *Filobasidium*, *Penicillium*, uncultured soil fungus, *Malassezia*, *Cryptococcus*, *Didymella*, *Rhodotorula*, *Eupenicillium*, *Coniochaeta*, uncultured Ascomycete	Park *et al.* (2012)
4	Skin mycobiome, skin swabs	Roche 454 n=10 Healthy individuals	*Malassezia (globosa, restricta, sympadialis)*, *Penicillium (chrysogenum, lanosum)*, *Aspergillus (candidus, terreus, versicolor)*, *Alternaria*, *Candida*, *Chaetomium*, *Chrysosporium*, *Cladosporium*, *Mucor*, *Rhodotorula*, *Trichophyton*	Findley *et al.* (2013)
5	Lung mycobiome; bronchoalveol-ar lavage and oropharyngeal wash	Healthy individuals Pyrosequencing 454	*Candida*, *Davidiellaceae*, *Cladosporium*, *Penicillium*, *Aspergillus*	Charlson *et al.* (2012)
6	Marine mycobiome, water and sediment sample	Pyrosequencing 454 n=56 (Pelagic and Benthic sample)	*Pezizomycetes*, *Agaricomycetes*, *Eurotiomycetes*	Tisthammer *et al.* (2016)
7	Soil mycobiome, seasonal sampling of of temperate oak (*Quercus petraea*) forest top soil	Pyrosequencing 454 n= 4 seasons	Autumn: *Mycosphaerella, Mucor, Geomyces, Umbelopsis, Lachnellula, Xenocomus* Spring: *Mycena, Cladophialophora, Meliniomyces* Summer: *Russula, Lactarius, Tomentella, Amanita, Hygrocybe* Winter: *Cryptococcus, Rhodotorula, Naevala, Fulvoflamma, Kriegeria*	Voriskova *et al.* (2013)
8	Plant mycobiome, wheat heads from two corners of field	Illumina sequencing n= 10	*Sporobolomyces roseus, Cladosporium cladosporiodes*, *Alternaria infectoria*	Hertz *et al.* (2016)
9	Rhizosphere mycobiome, *Crocus sativus*	Pyrosequencing 454 Rhizosphere samples during flowering stage	*Rhizopus* (46.62%), Uncultured genera (27.63%), *Mucor* (13.08%), *Moritiella* (3.12%)	Ambardar *et al.* (2016)
10	Needle mycobiome *Picea glauca*	Illumina sequencing n=48 trees Samples from treeline site and forest site	*Capnodiales*, *Pleosporales*, *Dothideales*, *Helotiales*, *Tremellales*	Eusemann *et al.* (2016)

Microbial communities are mostly dominated by bacteria and there is relatively less amount of fungal DNA. Secondly, paucity of reference database for complete fungal genome is also a drawback.

A second method is the targeted amplicon sequencing in which highly variable taxonomic marker ITS (Internal Transcribed Spacer) region is targeted and amplified and then compared with reference databases. For culture independent studies ITS region is amplified using PCR for mycobiome profiling. There are two ITS regions, ITS1 is located between 18S and 5.8S genes while ITS2 is located between 5.8S and 28S genes. Use of ITS marker for taxonomic classification is much similar to 16S rDNA region amplified to study bacterial community but differs in some respects. First, fungal ITS sequences of different species can differ widely in size and sequence content (Santamaria *et al.*, 2012). The ITS RNAs are degraded shortly after transcription and are not incorporated into the ribosome (Allmang *et al.*, 2000). Thus these regions are not conserved making it highly difficult to classify fungi to the species level. Second, there is no well established reference database of ITS sequences in fungi like 16S sequences for bacteria. Furthermore, ITS region generally provides insufficient taxonomic marker since known biological species are seldom grouped together within the same OTU (Schoch *et al.*, 2012). Whole genome sequencing is far beyond possibilities delivered currently

through sequencers like Illumina NextSeq and Hiseq since detecting fungi at species or even at subspecies level (10^{12}-10^{14} nucleotides per run) capacity is required (Zoll *et al.*, 2016).

Tang *et al.* (2015) applied combined sequencing and analysis approach to construct a manually curated reference database optimized for annotation of gastrointestinal fungi of 6-10 week old female C57BL/6J mice; they evaluated the strength and weaknesses of Illumina Miseq advantages over Ion Torrent PGM for analyzing intestinal mycobiomes. Miseq platform enabled identification of even the largest ITS1 fragments whereas Ion Torrent PGM failed to amplify longer amplicons. In order to use optimal primer set which induces least bias in the amplified sequence pool, researchers are therefore targeting regions apart from ITS. A study by Dollive *et al.* (2012) developed 18S rRNA gene amplicons that avoids mammalian and plant sequences and a flexible software pipeline (BROCC) to classify single cell eukaryotes. Another study by Asemaninejad *et al.* (2016) used a new set of primers targeting the D1 region of nuclear large subunit (LSU) ribosomal DNA. These workers achieved a greater depth of sequencing and the relative proportion of OTU recovered by LSU primers were more as compared to ITS2 primers.

INTERACTIONS AND FUNCTIONALITY

I. Intra-kingdom interaction (Mycobiome - Mycobiome): Mycobiome can influence ecosystem responses to the environment by interacting among themselves (**Table 2**). A recent study illustrated the complex and multidirectional interaction within mycobiome in a common disease like obesity (Rodriguez *et al*., 2015) where an inverse relationship was observed between the phylum *Ascomycota* with *Basidiomycota* and *Zygomycota* whereas, in non-obese patients a negative association was observed between *Pichiaceae* and *Dipodascaceae*. The finding of this study is in accordance with other studies on human subjects (Hoffmann *et al*., 2013; Mukherjee *et al.*, 2014). The importance of intra-kingdom interaction is associated with decrease in normal flora of skin like *Malassezia* in HIES patients and increased representation of opportunistic pathogens *Candida* and *Aspergillus* (Oh *et al.*, 2013). These findings suggest the existence of either positive or negative interaction in mycobiome which could be a result of immune modulation, dietary intake or complex interplay of mycobiome in host defense.

Table 2: Features of mycobiome and their reported functions

S. No.	Characteristic	Function of mycobiome	Reference
1.	Mycobiome abundance and diversity	Fungi thrive in nutrient rich environment as saprotrophs, parasites or symbionts. Abundance varies with the type of ecosystem , maximum being found in soil and lowest in marine. In plants mycobiome varies with the genotype and plant species and other abiotic factors. Around 390 fungal species recognized in human mycobiome and ≥80,000 species in soil.	Gouba and Drancourt (2015); Paey *et al*. (2016)
2.	Modulation of host immunity	Mutation in DECTIN -1, a pattern recognition receptor (PRR) encoding for C-type lectin present on innate immune cell in mice model resulted in tissue proliferation, weight loss, increased level of pro -inflammatory cytokines and gut inflammation. Dectin 1 receptor required for h omeostasis and immune development of host and interaction between mycobiome and intestinal cells of host.	Underhill and Iliev (2014)
3.	Nutrient acquisition	Fungi are essential in recycling of nutrients in all ecosystems because they are dominant decomposers of cellulose and lignin. Liberated nutrients are taken up by plants result ing in improved plant health. Mycorrhiza aid plants in uptake of nutrients and ectomycorrhizal fungus like *Laccaria bicolor* S238N and *Trichoderma virens* Gv. 29-8 increase lateral root growth.	Treseder and Lennon (2015); Davison *et al*. (2015)
4.	Prevention of colonization from pathogens	Involved in secretion of metabolites with antibiotic property and enzymes that inhibit the growth of pathogens. Host defense related genes are induced and expressed in *Theobroma cacao* by fungal leaf endophyte *Colletotrichum tropicale*	Meji'a *et al*. (2014)
4.	Interaction with microbiome	Bacterial and fungal communities influence each other negatively or positively. Long term antibiotic treatment led to robust expansion of *Candida* in gut.	Dollive *et al*. (2012)

II. Inter-kingdom interaction:

a) Bacteriome - Mycobiome: Inter-kingdom relationship exists between microbe-microbe as well as with host to modulate the ensuing effect. Though bacteria and fungi share similar niche there are several contrasting characteristics between microbiome and mycobiome (**Table 3**). The crosstalk between microbes is mediated by metabolic intermediates of anaerobic fermentation such as short chain fatty acids (SCFAs) produced by *Lactobacilli* which inhibit transition from budding to hyphal growth (Noverr and Huffnagle, 2004). Later, SCFAs are found to be involved in protecting epithelial lining by inducing the production of an antimicrobial peptide, cathelicidin LL-37, which is important in maintaining epithelial integrity (Otte *et al.*, 2009).

Table 3: A comparative assessment of mycobiome vs. microbiome

S. No.	Characteristic	Mycobiome	Microbiome
1.	Abiotic factors	Fungi can also survive in low pH indicating wider pH range for optimal growth; community composition weakly related to pH in soil (Rousk *et al*., 2010)	Bacteria can survive in narrow range of pH; community structure altered strongly with changes in soil pH (Rousk et al., 2010); other factors are more pronounced such as temperature at large spatial scale.
2.	Taxonomic classification	ITS groups fungus to a higher level taxa, genera or families	16 S marker is used with high taxonomic resolution even at species level
3	Diversity	Less diverse than microbiome; maximum in soil and lowest in marine environment. Fungi show greater heterogenity at local scales and less taxonomic overlap.	Microbiome is more diverse and abundant in all biomes
4.	Community assembly	Taxon richness of α communities of AM fungi decreases With latitude which is in contrast with other soil microbes (Davison *et al*., 2015)	Bacterial diversity is largely unrelated to changes in latiud e (Fierer and Jackson, 2005)
5.	Evolutionary diversification	Several marine *Ascomycota* and *Basidiomycota* lineages present are derived from terrestrial ecosystem (Richards *et al*., 2012)	Marine and terrestrial groups are evolutionary diverse (Richards *et al*., 2012)
6.	Niche selection	Selective presence of fungi at certain body site determined by site location (Findley *et al*., 2013)	Presence of bacteria determined more by site physiology (Findley *et al*., 2013)
7	Biogeographical patterns	Regional endemism, greater heterogenity and functional redundancy at local scales due to dispersal limitation (Tedersoo *et al*., 2014); less taxonomic overlap in endophytic fungi between rhizosphere and phylosphere of plants	Community composition is largely independent of ge ographic location. Lack of geographic structure in human microbiome; prevalent bactrial taxa are widespread across continents (Nasidze *et al*., 2009)

Candida is a resident of normal healthy mycobiome but transition of commensal form to pathogenic form is controlled by bacterial counterpart of microbiome. Jenkinson *et al.* (1990) reported intermicrobial binding between *C. albicans* and *Streptococci* in oral cavity. *Candida albicans* strongly influenced microbiota restoration after cefoperazone treatment after which Bacteroidetes and Synergistetes decreased significantly while Firmicutes remained unaltered (Erb *et al*., 2013). A positive correlation was reported between *Aspergillus fumigatus* and *Streptococcus* in cystic fibrosis patients where latter produced quorum sensing molecules for interaction between SMG members (*Streptococcus milleri* group) (Delhaes *et al*., 2012). A recent study by Hoffmann *et al*. (2013) extended the association of microbiome-mycobiome with archaea lineages. *Prevotella, Candida* and *Saccharomyces* were positively associated with *Methanobrevibacter* and were further correlated with high carbohydrate intake. Both the fungal genera were negatively associated with *Nitrososphaera* and absence of *Candida* with high intake of saturated fatty acids.

Apart from syntrophic association a study using model organism *C. elegans* showed that *Enterococcus faecalis* negatively regulated *Candida albicans* hyphal morphogenesis and biofilm formation (Cruz *et al*., 2013).

Similarly, reports on negative correlation are also supported for *Campylobacter* and *Candida* in HIV infected individuals (Mukherjee *et al.,* 2014) and *Candida* sp; *Aspergillus clavatus* and *Cryptococcus* dominance with decreased presence of *Saccharomyces cerevisiae* during Crohn's disease has also been reported (Li *et al*., 2014).

Agler *et al*. (2016) demonstrated the effect of pathogenic fungus *Albugo* and *Dioszegia* as hub microbes on stability of microbiome and significant changes in its absence. Hub microbes can influence diversity by acting indirectly via the host or directly through colonization efficiency of other microbes. Hubs are main targets of abiotic factors and transmit direct effect on the microbiome. Similar mechanisms might be controlling mycobiome structure but it remains to be elucidated in human system.

b) Microbiome-mycobiome-viriome: Most recently estimating bacteriophage population of human gut together with its role in inflammatory bowel disease (IBD) and bacterial dysbiosis have been described (Norman *et al.*, 2015). This work shows an inverse correlation between bacteriophage and bacterial diversity in IBD. Contributory role of enteric mycobiome and viriome in IBD provided evidence that the viriome-mycobime-microbiome and host interaction network exists which must be considered in future studies.

ROLE OF MYCOBIOME IN ECOLOGICAL FITNESS AND DISEASE

In soil ecosystem fungi play an important role in carbon sequestration therefore studying mycobiome becomes important to predict global environment change. Saprotrophic fungi and mycorrhizal fungi are most commonly found where former release extracellular enzymes and decompose organic matter whereas the latter is involved in carbon flow from plant root to soil. (Clenmenson *et al*., 2013).

Fungi such as, *Saccharomyces boulardii* possesses desirable traits to be used as probiotic as it interacts with resident microflora and protect mucosa as well as against enteric pathogens, neutralizes bacterial toxin and modulates cell signaling pathway (Zanello *et al*., 2009). Gastrointestinal disease IBD appears in two common forms, Crohn's disease and Ulcerative colitis. In Crohn's disease distinct mycobiome appears at the site of inflamed mucosa (Iliev *et al*., 2012; Li *et al.,* 2014; Chehoud *et al*., 2015) with decreased presence of non-pathogenic *Sacccharomyces*. These findings could find direct role in attaining healthy state either by supplementing the beneficial fungi or mycobiome manipulation since there is no association of bacteria with this disease. Similarly such interventions can also be applied to other diseases where altered mycobiome is observed such as GVHD (van der Veldon *et al*, 2013), Psoriasis (Paulino *et al*, 2006), etc. Altered mycobiome can also be used as a biomarker as shown by Chen *et al.* (2011) in four groups of healthy and diseased patients with different degree of hepatitis B cirrhosis. Increased fungal richness was positively correlated with disease progression or to distinguish between healthy non-healthy obesity (Rodriguez *et al.*, 2015).

In plant system complete community characterization could be helpful to improve the yield and quality significantly (Bai *et al*., 2015) of agriculturally important crop. Marine environments are relatively poor in nutrition but the diversity, ecology and physiology of fungi has recently been explored and revealed to contain novel lineages and metabolically active community in corals. Uncharacterized fungi could be a source of new drugs and diverse biotechnologically relevant discoveries (Amend *et al.*, 2012).

CONCLUSION

Uncovering the fungal diversity and realizing its importance as an integral part of microbiome is essential to have a broad outlook towards mycobiome. High throughput sequencing has unraveled greater diversity of fungi in previously unexplored ecosystems of earth thus expanding the culture collection of previously unclassified fungi. Fungi are colonizers of diversified habitats such as water, soil, air, litter, plants, etc. However, soil ecosystem is considered to harbour highest diversity of fungi compared to marine environments which contains low diversity. Fungal community exhibits strong biogeographical patterns and is affected by abiotic factors at spatial and temporal scales. At local scales, fungal communities are more diverse and functionally redundant and are least affected by geographical distance owing to the dispersal limitation of fungal spores. To understand whether fungal taxa overlap across habitat is still a matter of speculation. More understanding is needed to uncover the importance of fungi from microbial ecology perspective in terms of cross kingdom interaction (beneficial/ deleterious) and in niche selection. Additionally, functional analysis of mycobiome requires curated reference database and sequenced functional genes. An understanding of cross-kingdom microbial interactions within the context of health and disease holds considerable promise to facilitate the discovery of potential preventative and therapeutic targets.

Mycobiome has indirect implications on ecosystem fitness through interaction between different biomes and within biomes. Therefore, assessing these interactions can help to make personalized medicine, mycobiome manipulation, biomarker for diseases, etc possible in future. Furthermore, variations in mycobiome due to abiotic factors is an area where much more work remains to be done in elucidating the network of mycobiome which it shares with the microbiome. This could only be achieved after assessing the complete fungal diversity in an ecosystem. Thus, it could be concluded that focusing on one without considering the impact of the other could lead us to incomplete understanding of the existence of the networks.

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REFERENCES

Agler, M.T., Ruhe, J., Kroll, S., Morhenn, C., Kim, S.T., Weigel, D. Kemen, E. M. 2016. Microbial hub taxa

link host and abiotic factors to plant microbiome variation. *PLoS Biol.* **14**:e1002352. Doi:10.1371/journal.pbio.1002352.

Allmang, C., Mitchell, P., Petfalski, E. and Tollervey, D. 2000. Degradation of ribosomal RNA precursors by the exosome. *Nucleic Acids Res*. **28**:1684-91.

Ambardar, S., Singh H.R., Gowda, M. and Vakhlu, J. 2016. Comparative metagenomics reveal phylum level temporal and spatial changes in mycobiome of below ground parts of *Crocus sativus. PLoS ONE.* **11**:e0163300. doi:10.1371/journal.pone.0163300.

Amend, A.S. 2014. From dandruff to deep-sea vents: *Malassezia* like fungi are ecologically hyper-diverse. *PLoS Pathog*. **10**:e1004277

Amend, A.S., Barshis, D.J. and Oliver, T.A. 2012. Coral-associated marine fungi form novel lineages and heterogeneous assemblages. *The ISME J*. **6:**1291e1301.

Asemaninejad, A., Weerasuriya, N., Gloor, G.B., Lindo, Z. and Thorn R.G. 2016. New primers for discovering fungal diversity using nuclear large ribosomal DNA. *PloS ONE.* DOI:10.1371/journal.pone.0159043.

Bahram, M., Polme, S., Koljalg, U. and Tedersoo, L. 2010. A single European aspen (*Populus tremula*) tree individual may potentially harbour dozens of *Cenococcum geophilum* ITS genotypes and hundreds of species of ectomycorrhizal fungi. *FEMS Microbiol. Ecol.* **75**:313-320.

Bai, L., Cui, J., Jiea, W. and Cai, B. 2015. Analysis of the community compositions of rhizosphere fungi in soybeans continuous cropping fields. *Microbiol. Res*. **18**:49-56.

Balint, M., Bartha, L., O'Hara, R.B., Olson, M.S., Otte, J., Pfenninger, M., Robertson, A.L., Tiffin P. and Schmitt, I. 2015. Relocation, high-latitude warming and host genetic identity shape the foliar fungal microbiome of poplars. *Mol. Ecol.* **24**:235-248.

Bass, D., Howe1, A., Brown, N., Barton, H., Demidova, M., Michelle, H., Li L., Sanders H., Watkinson SC, Willcock, S. and Thomas A. Richards. 2007. Yeast forms dominate fungal diversity in the deep oceans. *Proc. R. Soc*. B **274**:3069-3077.

Berendsen, R.L., Pieterse, C.M.J. and Bakker, P.A.H.M. 2012. The rhizosphere microbiome and plant health. *Trends Plant Sci*. **17**:476-478.

Bik, E.M., Long, C.D., Armitage, G.C., Loomer, P., Emerson J, Mongodin, EF., Nelson, K.E., Gill, S.R., Fraser-Liggett, C.M. and Relman, D. 2010. Bacterial diversity in the oral cavity of 10 healthy Individuals. *The ISME J*. **4:**962-974.

Blackwell, M. 2011. The fungi: 1, 2, 3 … 5.1. 2011. million species? *Am. J. of Bot*. **98**:426-438.

Charlson, E.S., Diamond, J.M., Bittinger,K., Fitzgerald, A.S., Yadav, A., Haas, A.R. Bushman, F.D., Collman, R.G. 2012. Lung-enriched organisms and aberrant bacterial and fungal respiratory microbiota after lung transplant. *Am. J. Respir. Crit. Care Med.* **186**:536-545.

Chehoud, C., Lindsey, G., Albenberg, M.D., Judge, C., Hoffmann, C., Grunberg, S., Bittinger, K., Baldassano, R.N., Lewis, J.D., Bushman, F.D. and Wu, G.D. 2015. A fungal signature in the gut microbiota of pediatric patients with inflammatory bowel disease. *Inflamm. Bowel Dis*. **21**:1948-1956.

Chen, Y., Chen, Z., Guo, R., Chen, N., Lu, H., Huang, S., Wang, J. and Li, L. 2011. Correlation between gastrointestinal fungi and varying degrees of chronic hepatitis B virus infection. *Diagn. Microbiol. Infect. Dis.* **70:**492-498.

Clenmensen, K.E., Bahr, A., Ovaskainen, O., Dahlberg, A., Ekblad, A., Wallander, H., Stenlid, J., Finlay, R.D., Wardle, D.A. and Lindahl, B.D. 2013. Roots and associated fungi drive long-term carbon sequestration in boreal forest. *Sci.* **339:**1615-1618.

Cordier, T., Robin, C., Capdeville, X., Desprez-Loustau, M.L. and Vacher, C. 2012. Spatial variability of phyllosphere fungal assemblages: genetic distance predominates over geographic distance in a European beech stand (*Fagus sylvatica*). *Fungal Ecol.* **5**:509-520.

Cruz, M.R., Graham, C.E., Gagliano, B.C., Lorenz, M.C. and Garsin, D.A. 2013. *Enterococcus faecalis* inhibits hyphal morphogenesis and virulence of *Candida albicans*. *Infect. Immun.* **81**:189-200.

Cui, L., Morris, A. and Ghedin, E. 2013. The human mycobiome in health and disease. *Genome Med.* **5**:63. doi:10.1186/gm467.

Davison, J., Moora, M, Öpik, M., Adholeya, A., Ainsaar, L., Bâ, A., Burla, S., Diedhiou, A.G., Hiiesalu, I., Jairus, T., Johnson, N.C., Kane, A., Koorem, K., Kochar, M., Ndiaye, C., Pärtel, M., Reier, U., Saks, U., Singh, R., Vasar, M. and Zobel, M. 2015. Global assessment of arbuscular mycorrhizal fungus diversity reveals very low endemism. *Sci*. **349**:970-973.

Delhaes, L., Monchy, S., Fre´alle, E., Hubans, C., Salleron, J., Leroy, S., Prevotat, A., Wallet, F., Wallaert, B., Dei-Cas, E., Sime-Ngando T., Chabe, M. and Viscogliosi, E. 2012. The airway microbiota in cystic fibrosis: a complex fungal and bacterial community implications for therapeutic management. *PLoS ONE.* **7**:e36313. Doi:10.1371/journal.pone.0036313.

Dick, G. J., Andersson, A. F., Baker, B. J., Simmons, S. L., Thomas, B. C., Yelton, A. P. and Banfield, J.F. 2009. Community-wide analysis of microbial genome sequence signatures. *Genome Biol*. **10**:R85. doi: 10.1186/gb-2009- 10-8-r85.

Dietert, R.R. and Dietert, J.M. 2015. The microbiome and sustainable healthcare. *Healthcare.* **3**:100-129.

Dollive, S., Peterfreund, G.L., Mix, S.S., Bitinjer, K., Sinha, R., Hoffmann, C., Nabel, CS., Hill, D.A., Artis, D., Bachman, M.A., Custers-Allen, R., Grunberg, S., Wu, G.D., Lewis, J.D. and Bushman, F.D. 2012. A tool kit for quantifying eukaryotic rRNA gene sequences from human microbiome samples. *Genome Biol*. **13:**R60.

Duarte, S., Barlocher, F., Pascoal, C. and Cassio, F., 2016. Biogeography of aquatic hyphomycetes: current knowledge and future perspectives. *Fungal Ecol*. **19**: 169e181.

Dupuy, A.K., David, M.S., Li, L., Heider, T.N., Peterson, J.D., Montano, E.A., Bagtzoglou, A.D., Diaz, P.I. and Strausbaugh, L.D. 2014. Redefining the human oral mycobiome with improved practices in amplicon-based taxonomy: discovery of *Malassezia* as a prominent commensal. *PLoS ONE.* **9:**e90899. doi:10.1371/journal.pone.0090899.

Edgcomb, V.P., Beaudoin, D., Gast, R., Biddle, J.F. and Teske, A. 2011. Marine subsurface eukaryotes: the fungal majority. *Environ. Microbiol.* **13:**172-83.

Erb Downward, J.R., Falkowski, N.R., Mason, K.L., Muraglia, R. and Huffnagle, G.B. 2013. Modulation of post-antibiotic bacterial community reassembly and host response by *Candida albicans*. *Sci. Rep.* **3**:2191.

Eusemann, P., Schnittler, M., Nilsson, R.H., Jumpponen, A., Dahl, M.B., Wurth, D.G., Buras, A., Wilmking, M. and Unterseher, M. 2016. Habitat conditions and phenological tree traits overrule the influence of tree genotype in the needle mycobiome - *Picea glauca* system at an arctic treeline ecotone. *New Phytol*. doi 10.1111/nph.13988.

Ferguson, B.A., Dreisbach, T.A., Parks, C.G., Filip, G.M. and Schmitt, C.L. 2003. Coarse-scale population structure of pathogenic *Armillaria* species in a mixed-conifer forest in the Blue Mountains of northeast Oregon. *Can. J. For. Res*. **33**:612-623.

Fierer, N. and Jackson, R.B. 2005. The diversity and biogeography of soil bacterial communities. *Proc. Nat. Acad. Sci*. USA. **103**:626-631.

Findley, K., Oh, J., Yang, J., Conlan, S., Deming, C., Meyer, J.A., Schoenfeld, D., Nomicos, E. and Park, M. 2013. NIH Intramural Sequencing Center Comparative Sequencing Program, Kong HH, Segre JA: Topographic diversity of fungal and bacterial communities in human skin. *Nature.* **498**:367-370.

Gao, Z., Li, B., Zheng, C. and Wang, G. 2008. Molecular detection of fungal communities in the Hawaiian marine sponges *Suberites zeteki* and *Mycale armata*. *Appl. Environ. Microbiol*. **74**:6091-6101.

Ghannoum, M.A., Jurevic, R.J., Mukherjee, P.K., Cui, F., Sikaroodi, M., Naqvi, A. and Gillevet, P.M. 2010. Characterization of the oral fungal microbiome (mycobiome) in healthy individuals. *PLoS Pathog.* **6**:e1000713. doi:10.1371/journal.ppat.1000713.

Gouba, N. and Drancount, M. 2015. Digestive tract mycobiota: a source of infection. *Med. Mal. Infect.* **45:**9-16.

Guo, X., Zhang, Q., Zhang, X., Zhang, J. and Gong, J. 2015. Marine fungal communities in water and surface sediment of a sea cucumber farming system: habitat-differentiated distribution and nutrients driving succession. *Fungal Ecol.* **14**:87e98.

Hallen-Adams, H.E., Kachman, S.D., Kim, J., Legge, R. and Martínez, I. 2015. Fungi inhabiting the healthy human gastrointestinal tract: A diverse and dynamic community. *Fungal Ecol*. **15**:9-17.

Hertz, M., Jensen, J.R., Jensen, L.O., Thomsen, S.N., Winde, J., Dueholm, M.S., Sorensen, L.H., Wollenberg, R.D., Sorensen, L.H., Wollenberg, R.D., Sorensen, H.O., Sondergaard, T.E. and Sorensen, J.L. 2016. The fungal community changes over time in developing wheat heads. *Int. J. Food Microbiol.* **222**:30-39.

Hoffmann, C., Dollive, S., Grunberg, S., Chen, J., Li, H., Wu, G. D., Lewis, J. D. and Bushman, F.D. 2013. Archaea and fungi of the human gut microbiome: correlations with diet and bacterial residents. *PLoS ONE.* **8**:e66019.

Huffnagle, G.B. and Noverr, M.C. 2013. The emerging world of the fungal microbiome. *Trends Microbiol.* **21**:334-341.

Hug, L.A., Baker, B.J., Anntharaman, K., Brown, C.T., Probst, A.J., Castelle, C.J., Butterfield, C.N., Hernsdorf, A.W., Amano, Y., Ise, K., Suzuki, Y., Dudek, N., Relman, D.A., Finstad, K.M., Amundson, R., Thomas, B.C. and Banfield, J.E. 2016. A new view of the tree of life. *Nat. Microbiol*. **1**:1-6 doi 10.1038/NMICROBIOL.2016.48.

Huttenhower, C., Gevers, D., Knight, R., Abubucker, S., Badger, J.H., Chinwala, A.T. *et al*. 2012. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature.* **486**:207-214.

Iliev, I.D., Funari, V.A., Taylor, K.D., Nguyen, Q., Reyes, C.N. Strom, S.P, Brown, J., Becker, C.A., Fleshner, P.R., Dubinsky, M., Rotter, J.I., Wang, H.L., McGovern, D.P., Brown, G.D. and Underhill, D.M. 2012. Interactions Between Commensal Fungi and the C-Type Lectin Receptor Dectin-1 Influence Colitis. *Sci.* **336**:1314-1317.

Jenkinson, H.F., Lala, H.C. and Shepherd, M.G. 1990. Co-aggregation of *Streptococcus sanguis* and other streptococci with *Candida albicans*. *Infect. Immun*. **58:**1429-1436.

Jones, M.D.M., Forn, I., Gadelha, C., Egan, M.J., Bass, D., Massana, R. and Richards, T.A. 2011. Discovery of novel intermediate forms redefines the fungal tree of life. *Nature*. **474**: 200-203.

Jumpponen, A. and Brown, S.P. 2014. The rich and the sensitive: diverse fungal communities change functionally with the warming Arctic. *Mol. Ecol.* **23**: 3127-3129.

Jumpponen, A. and Jones, K.L. 2010. Seasonally dynamic fungal communities in the *Quercus macrocarpa* phyllosphere differ between urban and nonurban environments. *New Phytol*. **186:** 496-513.

Landenmark, H.K.E., Forgan, D.H. and Cockell, C.S. 2015. An estimate of the total DNA in the biosphere. *PLoS Biol*. **13**:e1002168. Doi:10.1371/journal.pbio. 1002168.

Le Calvez, T., Burgaud, G., Mahe, S., BArbier, G. and Vandenkoornhuyse, P. 2009. Fungal diversity in deep sea hydrothermal ecosystems. *Appl. Environ. Microbiol.* **75**:6415-6421.

Li, Q., Wang, C., Tang, C., He, Q., Li, N. and Li, J. 2014. Dysbiosis of gut fungal microbiota is associated with mucosal inflammation in Crohn's disease. *J. Clin. Gastroenterol.* **48**:513-523.

Lindahl, B.D., Ihrmark, K., Boberg, J., Trumbore, S.E., Högberg, P., Stenlid, J. and Finlay, R,D. 2007. Spatial separation of litter decomposition and mycorrhizal nitrogen uptake in a boreal forest. *New Phytol*. **173**:611-620.

Locey, K.J. and Lennon, J.T. 2016. Scaling laws predict global microbial diversity. *Proc. Natl. Acad. Sci.* USA. **113**:5970-5975. http://dx.doi.org/10.1073/ pnas.152191113.

Manoharachary, C., Sridhar, K., Singh, R., Adholeya, A., Suryanarayanan, T.S., Rawat, S. and Johri, B.N. 2005. Fungal biodiversity: Distribution, conservation and prospecting of fungi from India. *Curr. Sci*. **89**:58-72.

Massana, R. and Pedr ´ os-Ali ´o, C. 2008. Unveiling new microbial eukaryotes in the surface ocean. *Curr. Opin. Microbiol.* **11**:213-18.

Mejı´a, L.C., Herre, E.A., Sparks, J.P., Winter, K., Garcı´a, M.N., van Bael, S.A., Stitt, J., Shi, Z., Zhang, Y., Guiltinan, M.J. and Maximova, S.N. 2014. Pervasive effects of a dominant foliar endophytic fungus on host genetic and phenotypic expression in a tropical tree. *Front. Microbiol*. **5**:479.

Morgan, X.C. and Huttenhower, C. 2012. Chapter 12: Human microbiome analysis. *PLoS Comput. Biol*. **8**:e1002808. doi:10.1371/journal.pcbi.1002808

Morris, C.E. and Kinkel, L.L. 2002. Fifty years of phyllosphere microbiology: significant contributions to research in related fields. In: *Phyllosphere Microbiology* (Eds.: Lindow, S.E., HechtPoinar, E.I., and Elliott, V.J.). Am. Phytopathol. Soc. St Paul, pp. 365e375.

Mukherjee, P.K., Chandra, J., Retuerto, M., Sikaroodi, M., Brown, R.E., Jurevic, R., Salata, R.A. Lederman, M.M., Gillevet, P.M. and Ghannoum, M.A. 2014. Oral mycobiome analysis of HIV-infected patients: identification of *Pichia* as an antagonist of opportunistic fungi. *PLoS Pathog.* **10**:e1003996.

Norman, J.M., Handley, S.A., Baldridge, M.T., Droit, L., Liu, C.Y., Keller, B.C., Kambal, A., Monaco, C.L., Zhao, G., Fleshner, P., Stappenbeck, T.S., McGovern, D.P.B., Keshavarzian, A., Mutlu, E.A., Sauk, J., Gevers, D., Xavier, R.J., Wang, D., Parkes, M. and Virgin, H.W. 2015. Disease-specific alterations in the enteric virome in inflammatory bowel disease. *Cell*. **160**:447-60.

Noverr, M.C. and Huffnagle, G.B. 2004. Regulation of *Candida albicans* morphogenesis by fatty acid metabolites. *Infect. Immun.* **72**: 6206-6210.

Oever, J.T. and Netea, M.G. 2014. The bacteriome-mycobiome interaction and antifungal host defense. *Eur. J. Immunol*. **44**:3182-3191.

Oh, J., Freeman, A. F., Program, N. C. S., Park, M., Sokolic, R., Candotti, F., Holland, S. M. Segre, J.A., and Kong, H.H. 2013. The altered landscape of the human skin microbiome in patients with primary immunodeficiencies. *Genome Res*. **23**:2103-2114.

Orsi, W., Biddle, J.F., Edgcomb, V. 2013. Deep sequencing of subsea floor eukaryotic rRNA reveals active fungi across marine subsurface provinces. *PLoS ONE*. **8**:e56335.

Otte, J.M., Zdebik, A.E., Brand, S., Chromik, A.M., Strauss, S., Schmitz, F., Steinstraesser, L. *et al*. 2009. Effects of the cathelicidin LL-37 on intestinal epithelial barrier integrity. *Regul. Pept*. **156**:104-117.

Park, H.K., Ha, M.H., Park, S.G., Kim, M.N., Kim, B.J. and Kim, W. 2012. Characterization of the fungal microbiota (mycobiome) in healthy and dandruff-afflicted human scalps. *PLoS ONE.* **7**:e32847.

Paulino, L.C., Tseng, C.H., Strober, B.E. and Blaser, M.J. 2006. Molecular analysis of fungal microbiota in samples from healthy human skin and psoriatic lesions. *J. Clin. Microbiol*. **44**:2933-2941.

Peay, K.G., Kennedy, P.G. and Talbot, J.M. 2016. Dimensions of biodiversity in the Earth mycobiome *Nature Rev. Microbiol.* **14**:434-447.

Qin, J., et al. 2010. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. **464**:59-65.

Rama, T., Norden, J., Davey, M.L. and Mathiassen, G.H. 2014. Fungi ahoy! Diversity on marine wooden substrata in the high North. *Fungal Ecol*. **8**:46-58.

Richards, T.A., Jones, M.D.M., Leonard, G. and Bass, D.,

2012. Marine fungi: their ecology and molecular diversity. *Annu. Rev. Mar. Sci.* **4**:495e522.

Rodríguez, M.M., Pérez, D, Chaves, F.J., Esteve, E., Marin-Garcia P., Xifra, G., Vendrell, J., Jové M., Pamplona, R., Ricart, W., Portero-Otin, M., Chacón M.R. and Fernández, J.M. 2015. Real obesity changes the human gut mycobiome. *Sci. Rep*. **5**:14600 | DOI: 10.1038/srep14600.

Roth, R.R. and James, W.D. 1988. Microbial ecology of the skin. *Annu. Rev. Microbiol*. **42**:441-464.

Rousk, J., Baath, E., Brookes, P.C., Lauber, C.L., Lozupone, C., Caporaso, J.G., Knight, R. and Noah, F. 2010. Soil bacterial and fungal communities across a pH gradient in an arable soil. *The ISME J*. **4**:1340-1351.

Santamaria, M., Fosso, B., Consiglio, A., De Caro, G., Grillo, G., Licciulli, F., Liuni, S., Marzano, M., AlonsoAlemany, D., Valiente, G. and Pesole, G. 2012. Reference databases for taxonomic assignment in metagenomics. *Brief. bioinform*. **13**:682-95.

Sapkota, R., Knorr, K., Jorgensen, L.N., O'Hanlon, K.A. and Nicolaisen, M. 2015. Host genotype is an important determinant of the cereal phyllosphere mycobiome. *New Phytol*. doi 10.111/nph.13418.

Schoch, C.L., Seifert, K.A. Huhndorf, S., Robert, V., Spouge, J.A., Levesque, C.A., and Chen, W. 2012. Nuclear ribosomal internal transcribed spacer (ITS) region as a universal DNA barcode marker for fungi. *Proc. Natl. Acad. Sci.* U.S.A. **109**:6241-6246.

Sender, R., Fuchs, S. and Milo, R. 2016. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*. **14**:e1002533 DOI:10.1371/journal.pbio. 1002533.

Serna-Chavez, H., Fierer, N. and van Bodegom, P.M. 2013. Global drivers and patterns of microbial abundance in soil. *Glob. Ecol. Biogeogr*. **22**:1162-1172.

Simoes, M.F., Antunes, A., Ottoni, C.A., Amini, M.S., Alam, I., Alzubaidy, H., Mokhtar, N.A., Archer, J.A.C. and Bajic, V.B. 2015. Soil and rhizosphere associated fungi in gray mangroves (*Avicennia marina*) from the red Sea- A metagenomic approach. *Gen. Prot. Bioinfo*. **13**:310-320.

Talbot, J. M., Brunsb, T.D., Taylorb , J.W., Smitha, D.P., Brancob, S., Glassmanb, S.I., Erlandsona, S., Vilgalysc, R., Liaoc, H.L., Smithd, M.E. and Peaya, K.G. *2014.* Endemism and functional convergence across the North American soil mycobiome. *Proc. Natl Acad. Sci. USA*. **111**:6431-6346.

Tang, J., Iliev, I.D., Brown, J., Underhill, D.M. and Funari, V.A. 2015. Mycobiome: approaches to analysis of intestinal fungi. *J. Immunol. Methods*. **421**:112-121.

Tardy, V., Spor, A., Mathieu, O., Lévèque, J., Terrat, S., Plassart, P., Regnier, T., Bardgett, R. D., van der Putten, W. H., Roggero, P.P., Seddaiu, G. 2015. Shifts in microbial diversity through land use intensity as drivers of carbon mineralization in soil. *Soil Biol. Biochemist.* **90**:204-213.

Tedersoo, L., Bahram, M., Põlme, S., Kõljalg, U., Yorou, N.S., Wijesundera, R., Ruiz, L.V., Vasco-Palacios, A.M., Thu, P.Q., Suija, A., Smith, M.E., Sharp, C., Saluveer, E. *et al*. 2014. Global diversity and geography of soil fungi**.** *Sci*. **346**:1078- 1088.

Tisthammer, K.H., Cobian, G.M. and Amend, A.S. 2016. Global biogeography of marine fungi is shaped by the environment. *Fungal Ecol*. **19**:39-46.

Treseder, K.K. and Lennon, J.T. 2015. Fungal traits that drive ecosystem dynamics on land. *MMBR*. **79:**243-263.

Underhill, D.M. and Iliev, I.D. 2014. The mycobiota: interactions between commensal fungi and the host immune system. *Nat. Rev. Immunol.* **14**:405-416.

Unterseher, M., Siddique, A.B., Brachmann, A. and Person, D. 2016. Diversity and composition of the leaf mycobiome of beech (*Fagus sylvatica*) are affected by local biochemistry. *PLoS ONE*. **11**:e0152878. Doi: 10.1371/journal.pone.0152878.

van der Velden, W.J., Netea, M.G., de Haan, A.F., Huls, G.A., Donnelly, J.P. and Blijlevens, N. 2013. Role of the mycobiome in human acute graft-versus-host disease. *Biol. Blood Marrow Transplant*. **19**:329 - 332.

Voriskova, J., Brabcova, V., Cajtham, T. and Baldrian, P. 2013. Seasonal dynamics of fungal communities in a temperate oak forest soil. *New Phytol*. **201**:269-278.

Warinner, C., Rodrigues, J.F.M., Vyas, R., Trachsel, C. and Shved, N. 2014. Pathogens and host immunity in the ancient human oral cavity. *Nat. Genet*. **46**:336-344.

Zanello, G., Meurens, F., Berri, M. and Salmon, H. 2009. *Saccharomyces boulardii* effects on gastrointestinal diseases. *Curr. Issues Mol. Biol*. **11**:47-58.

Zoll, J., Snelders, E., Verweij, P.E. and Melchers, W.J.C. 2016. Next generation sequencing in the mycology lab. *Curr. Fungal Infect. Rep*. **10**:37-42.