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Review articles

The mycobiome – a friendly cross-talk between fungal colonizers and their host

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ABSTRACT. The organisms colonizing a living host create together with their host a holobiome. The holobioms are networks of mutualistic interactions between host`s cells and microorganisms communities. The fungi are among these microorganisms and have been also well known to infect human and animals. These organisms are associated with a wide range of diseases as superficial or systemic mycoses. Fungi as colonizers can also modify host physiology and metabolism, energy acquisition, vitamin-cofactor availability, development and function of immune system, and even host behavior. The objective of this review is to familiarize with recent data concerning the role of fungi creating mammalian mycobiome in the maintenance of the host health status.

Key words: Fungi, holobiome, mycobiome, microbiota

Introduction

Colonizing organisms are known to play an important role in the innate and adaptive immune responses of the host, as well as exerting an influence on barrier function and metabolic parameters. In return, host reactions and immune responses also influence the composition of the microbiota [1]. Fungi constitute the most significant group of colonizers and are believed to be the most environmentally abundant eukaryotes, with an estimated 1.5 million species, however many are not cultivable outside of their natural niches, and only about 1–5% of the species have been well described. Fungi are known to infect human and animals and have been associated with a wide range of diseases termed superficial or systemic mycoses. As was described by Seed [2], fungi can modify host physiology and metabolism, energy acquisition, vitamin-cofactor availability, the development and function of the immune system, and even host behavior. The interactions between the fungi and other microorganisms and their influence on host physiology have been demonstrated in many studies concerning their implications on health and disease [3].

The objective of this review is to summarize recent data concerning the topic outline the role of fungi within the mammalian mycobiome as a part of the holobiome, and to clarify their role in the health status of the host.

The holobiomes of hosts are networks of mutualistic interactions between host cells and the bacteria and fungi communities that colonize the host itself. The term "**microbiota**" was first used to describe the community of microorganisms living in the host body space by American molecular biologist and Nobel laureate Joshua Lederberg. He also highlighted the significant role played by microorganisms inhabiting the host in its health. The human body contains over 10 times more microbial cells than its own cells [4]. It has been stated that microbiome and host emerged as a unity along evolution by a process of integration. The immune system should tolerate the colonization of commensal bacteria and fungi but defend itself against invasion by them.

It is now well known that the human microbiome may play a role in autoimmune diseases as diabetes, fibromyalgia, multiple sclerosis, arthritis and some cancer [1,3,4]. Gut microbes may also aggravate common obesity. Some microorganisms can modify the production of neurotransmitters in the host and thus may be associated with the occurrence of schizophrenia, depression or bipolar disorder [5–7]. Spirillum *Borrelia burgdorferi* causes Lyme disease which can provoke depression [8]. Autistic people have a unique microbiome typified by a much higher proportion of *Clostridium* species then healthy individuals. Children with gastrointestinal dysfunction were found to have the bacteria *Suterella,* which is absent in non-autistic children with the same problem [9–12]. It is known that the composition of the human microbiome is highly variable both within a single and between different individuals.

The term "**microbiome**" or "**holobiome**" should be used to refer to the collection of genomes of microorganisms in a biosystem (host) and "**microbiota**" should be used to refer to the collection of organisms [4]. The hologenome theory proposes that an object is not an individual organism, but an organism together with its associated microbial communities. According to this hypothesis, a dynamic relationship exists between hosts and their symbiotic microbial communities. By altering its composition, this "**holobiont**" can adapt to changing environmental conditions far more rapidly than by genetic mutation and selection alone. Fungi exist as part of this community as a "**mycobiota**" and constitute a "**mycobiome"** [1,4–7].

The mycobiome differs between host type, their body sites and between individuals. The mycobiota has been studied in animals ranging from ruminants to insects, such as wasps [13] and termites, and humans [14]. The results suggest that fungal communities are stable across time and are personalized [15]. Employing next-generation sequencing molecular method allows rare taxa of fungi to be detected in mycobiome. The first culture-independent analysis of the mycobiota of the mammalian intestine revealed previously unknown diversity and abundance for fungal species. However, investigations of mouse gastrointestinal tract [16] found that fungi only constitute approximately 2–3% of the total community of a mucous biofilm.

Microbial intestinal eukaryotes have also been suggested as one of the causative agents of diseases such as irritable bowel syndrome, inflammatory bowel disease (IBD), and "leaky gut" syndrome [10,15,17]. Although the commensal fungi are essential members of human ecosystems, their role in the maintenance of health can be understood only through an integrated ecological approach. Metagenomic studies of changes in the metabolite profiles associated with microbiota indicate that some bacterial species contribute to host-fungal symbiosis and mucosal homeostasis [10,15,17] .

Does the host "feel" fungi?

The participation of microbiota in stimulation of the host's immunity and metabolic activities indicates that the interactions between fungi and their hosts are more complex than previously understood. It is clear that interactions between host, fungus and the other members of the microbiota create the host-fungus relationship: for example, microbial dysbiosis predisposes to chronic fungal infections or diseases at local sites. A basic element of the immune response to fungi is that of the PRRs (pattern recognition receptors), which are part of the immune system. These are proteins expressed by cells of the innate immune system which are able to identify two classes of molecules: pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs), which are associated with cell components and are released during cell damage or death. Several PRRs, including TLR-2, TLR-4, dectin-1, dectin-2, and galectin-3 on phagocytes specifically recognize fungal PAMPs such as α-mannans, β-mannans, chitin and β-glucans or nucleic acids (DNA), and peptides such as microtubule elongation factors, as well as peptidoglycans and lipoteichoic acids from Gram-positive bacteria. DAMPs match with a number of compounds including uric acid and extracellular ATP [12]. PRRs may be divided into two types of receptors: endocytic and signaling PRRs. The former promote the destruction of microorganisms by phagocytes without relaying an intracellular signal while the latter, include large families of membrane-bound Toll-like receptors which recognize extracellular or endosomal pathogen-associated molecular patterns and cytoplasmic NOD-like receptors. NOD-like receptors (NLRs) are cytoplasmic proteins that regulate inflammatory and apoptotic responses. Toll-like receptors (TLRs)

stimulate the synthesis and secretion of cytokines, and activate other host defense compounds necessary for innate or adaptive immune responses, such as C-type lectin receptors, the galectin family of proteins to trigger intracellular signaling cascades [12,18–20].

The immune system does not ignore commensal or opportunistic fungi but recognises different fungi through PRRs and gives rise to the symbiotic host-fungal relationship. This balance may be fluid, and ranges between tolerogenic or pro-inflammatory responses. By sensing the conserved molecular structures on fungi (PAMPs), PRRs promote the activation of the immune system and eventually the clearance of fungi. Following the recognition of this pattern, macrophages and dendritic cells mature and activate T cells through an antigen-presenting process. Depending on which cytokines are stimulated, activated T cells differentiate into either Th-1, which promotes the phagocytosis of fungi, or Th-2, which activates B cells to produce of fungus-specific antibodies [12,18–21]. Monocytes, macrophages, neutrophils and epithelial and endothelial cells contribute to the antifungal innate immune response through phagocytosis and killing of pathogens. The uptake of fungi by dendritic cells (DCs) promotes the differentiation of naive T cells into effector Th-cell subtypes [19].

The interaction between fungi and the host depends on several Ag-specific adaptive immune responses. The production of IFN-γ by Th1 lymphocytes is fundamental for stimulating the antifungal activity of neutrophils. Although some research indicates that IL-17-producing T cells play a pathological role in autoimmune diseases, other studies suggest Th17 cells may play a protective role in fungus-induced host defence, as T-cell polarization is caused by PAMP stimulation [19,22,23].

The Human Mycobiome is believed to be derived from the mother material vaginal mycobiota. The vaginal microbiome is a rich community and is well studied with regard to bacterial constituents [2,12,19]. More than 50% of the fungal constituents are Ascomycota, the majority Saccharomycetales, the most abundant being 16 different original taxonomic units of *Candida* spp. Other Ascomycota including *Cladosporium*, *Eurotium*, *Alternaria* and the Basidomycote *Rhodotorula*, were present as only 1–2% of the total composition. A large percentage of the total mycobiome sequences were unclassified within the fungal kingdom. The passage of the newborn through the vaginal canal is the first major exposure to the microorganisms of which the earliest colonizers are the fungal components. However, transmission to the newborn is not well documented, and assembly of additional environmental fungi into the microbiome has not been monitored in the healthy infant. Infants born eight or little more weeks before term and weighing less than 1500 g at birth are at significantly increased risk of invasive fungal disease, primarily by *Candida* species. Together with the premature nature of their intestinal and systemic immunity, other factors such as broad antibiotic exposure put the infants at greater risk of *Candida* colonization and infection. Culture-based data suggests more than 50% of early born infants present intestinal colonization with *Candida* spp. The development and maintenance of the mycobiome during early life remains unclear, together with susceptibility to external factors, including nutritional stresses, metabolic alterations such as diabetes and obesity, and host inflammatory disorders as well as exposure to xenobiotic factors and microbe-destruction agents such as anti-infective host-supplemented agents [2,12,19].

Mycobiome molecular investigation

The fungi distributed on and within the body are usually investigated in association with infectious diseases and allergies. Fungi are present in the niches of the human body in much lower numbers than bacteria, which are abundant in the digestive tract and on the skin. Although fungi constitute less than 0.1% of the total microbiota [24], the fungal constituents of the microbiome may play key roles in maintaining microbial community structure and metabolic function.

To investigate the microbiome and mycobiome, studies have sequenced the total DNA, both host and microbial. Microbial genome data was obtained by identifying the bacterial specific ribosomal 16S rRNA and two regions have been most frequently used for fungal studies, the first being the 18S rRNA sequence, and the second being the 5.8S and 28S rRNA internal transcribed spacer regions (ITS) which are found within the 18S sequence. Reference databases have been established for each sequence type. Multiple sequencing technologies have been used for sequencing and differentiating the mixtures of amplicons.

The constitution of the microbiome may also be determined through the sequencing and analysis of total genomic DNA, or by the use of shotgun metagenomics and metatranscriptomics [24]. In metagenomics sequencing, DNA is recovered directly from environmental samples in an untargeted manner with the goal of obtaining samples of all genes of all members of the community. Metatranscriptomics studies have been performed to study the gene expression of microbial communities through methods such as the pyrosequencing of extracted RNA. Structure based studies have also identified non-coding RNAs (ncRNAs) such as ribosome from microbiota. Metaproteomics is a new approach that studies the proteins expressed by microbiota [24,25].

Fungal colonization of different body niches

Fungi can colonize different biocompartments opportunistically in individuals who come in contact with them in outdoor environments, where fungi are ubiquitous or in indoor environments, where fungi are found on food, in the air and many home surfaces.

The skin

The skin is the largest organ of the body, and its functions include protecting the body from pathogens, preventing loss of moisture and the regulation of body temperature. Scraping and swabs have been used to study the skin mycobiome, focusing on the wide variety of dry, moist, and oily sites distributed across the surface of the body. Considered as an ecosystem, the skin is a basis for microbial communities that live in niches. The hair scalp or naked skin are quite different niches. Studies of the microbiota that inhabit these different niches may reveal the balance between health skin and disease. Many cutaneous disorders such as atopic dermatitis (AD) have been associated with microbiota [26–29]. Recent metagenomics studies, investigating the bacterial and fungal components of the human skin microbiota of healthy subjects, have uncovered surprising differences in microbial diversity between distinct topographical skin sites. In general, the skin is dominated by *Malassezia* fungi, but some niches including the human foot exhibit a broad fungal diversity, with the presence of a wide range of fungal genera including *Rhodotorula*, *Debaromyces*, *Cryptococcus*, and *Candida* [27]. These results demonstrate that physiologic attributes and topography of the skin niches may influence on the composition of the mycobiota. In this complex homeostasis, keratinocytes, which express many PRRs, such as the TLR family, have a key role in the innate immune response against pathogens. As a direct response to microbes, or through indirect activation by cytokines such as IL-22, keratinocytes can produce a wide array of antimicrobial peptides such as beta-defensin and the cathelicidin LL-37 [29]. Langerhans cells (LCs) contribute to priming adaptive T-cell immunity to skin pathogens such as yeast (*C. albicans*) favoring the induction of Th17-cell responses by direct Ag presentation to Th17 cells. [21,27,29]

The skin can be a point of entry for fungal infections when the epithelial barrier is breached, or it can be a site for disseminated, systemic fungal diseases. For example, the dryness associated with AD compromises the barrier function of the skin and as a result AD is associated with high susceptibility to viral, bacterial, and fungal skin infections. Although *Malassezia* yeasts are a part of the mycobiota of healthy skin, they have also been associated with a number of diseases affecting the skin, such as *pityriasis versicolor*, *folliculitis*, *seborrhoeic dermatitis* and dandruff, and canine‘ “hot spot” [2,28,30].

Oral cavity

The oral microbiota is a critical component of health and disease. The oral cavity is the major portal of entry into the digestive and respiratory tracts. It is a complex environment for microbial community formation and it is dynamically changed as response to external conditions. For the oral mycobiome, sample collection may include oral washes from which cells may be collected by centrifugation. Gingival and buccal scrapings are also complementary approaches for this purpose.

Few fungi were previously believed to inhabit the oral cavity [2]; however, by the use of multitag pyrosequencing approach combined with pan-fungal internal transcribed spacer (ITS) primers, Ghannoum et al. [31] found that the distribution of fungal species in the mouth varied greatly between different hosts. The mycobiota of a healthy human mouth consists of 74 cultivable and 11 non-cultivable fungal genera. The fungal mycobiota is typically composed primarily of *Candida* species

(75%) followed by *Cladosporium* (65%), *Aureobasidium* (50%), *Saccharomyces* (50%), *Aspergillus* (35%), *Fusarium* (30%), and *Cryptococcus* (20%). The molecular investigation showed that *Candida*, *Saccharomyces*, *Penicillium*, *Aspergillus*, *Scopulariopsis*, and *Genotrichum* were among those previously reported. Fungal genera and species associated with invasive diseases, including *Aspergillus*, *Cryptococcus*, *Fusarium* and *Alternaria* were also identified, indicating that some potentially pathogenic species are present in the oral mycobiome even during a state of health. The oral fungal genera categorized as "non-cultivatable" and not previously taxonomically classified were confirmed in "Fungal Metagenomics Project ITS sequence database" and the no cultivable group constituted 50% or more of the fungi identified.

A genome-based investigation analysis of 18S ITS sequences (CloVR-ITS) of the composition and diversity of fungal communities in human oral biocompartments, provided by Dupuy et al. [32,33] confirmed the genus-level composition of the oral mycobiome, which consist of *Alternaria*, *Aspergillus*, *Candida*, *Cladosporium*, *Cryptococcus*, *Fusarium*, *Aureobasidium*, *Saccharomyces*, *Epicoccum* and *Phoma.* Most unexpectedly, *Malassezia* species was found to be the predominant commensal in saliva. These findings studies have forced a re-evaluation of the current conception of the oral mycobiome, especially with the discovery of the high prevalence and abundance of the genus *Malassezia*. Previously known as an inhabitant and important pathogen of the skin, it has recently been reported as the predominant fungal genus in the nostril and on the back of the head and ear. This study suggests the existence of many consensus members of the core mycobiome, and of unique patterns for individuals. The lists of community members may be long; however, they may enhance the biological relevance of sequence-based fungal surveys, and may represent a good basis for understanding the role of fungi in health and all disease. Culture-based methods have not detected *Malassezia* species due to their need for lipids and all specialized culture media for fungal growth [32,33].

Infections with *Candida* spp. are well known in patients with HIV and may precede invasive infections of the esophagus or the bloodstream [33]. The main bacterial taxa are known to be similar between healthy subjects and patients, whereas the fungal taxa differed significantly. Species of *Candida*, *Aspergillus*, and *Fusarium* were more abundant in the oral mycobiome among the HIV-infected patients, while *Pichia* and *Candida* were common in the healthy subjects. *Pichia* in cultures is able to inhibit *Candida* hyphae formation necessary to start the invasive form of disease. The presence of fungal pathogens in the oral cavity of healthy individuals is quite unexpected and its clinical relevance is unknown. The pathogenicity of the fungi in the oral environment may be controlled in healthy individuals by other fungi as well as by the functional immune system, suggesting that interdependent cross-talk may exist between constituents of the oral mycobiota [2,19,32,33].

The gut mycobiome

For the human intestinal mycobiome, faeces are most frequently used as a convenient and non-invasive source from which is possible to obtain an overview of the types of organisms present in the digestive tract. The intestinal microbiome contains the greatest quantity and diversity of the microorganisms with an estimated one trillion organisms [2,24]. The intestinal microbiome has been implicated to act on local and systemic metabolism, immune system maturation and function, behaviour and even diseases in many systems. Although the bacterial constituents of the gut-associated microbiome have been often studied, the diversity and function of gut-associated fungi is less known (Fig. 1).

Infant faeces have a diverse fungal constituency. The most abundant order is known to be the Saccharomycetales, with at least six different species of *Candida*, four different species of *Cladosporium*, three different predicted species of *Cryptococcus*, and *Saccharomyces cerevisiae*. Also present in most investigated samples were the Malasseziales, Eurotiales, Botryosphaeriales and Filobasidiales.

The mycobiome of the canine intestinal tract has also been studied. A total of five phyla were identified: the Ascomycota and Basidiomycota were found in more than half of the tested dogs, equally in healthy animals and those suffering from digestive tract disorders [34], while the Chytridiomycota, Neocallimastigomycota and Microsporidia were found in half the tested dogs in both groups. A total of 219 fungal genera were identified across all investigated dogs. No significant differences were found in the

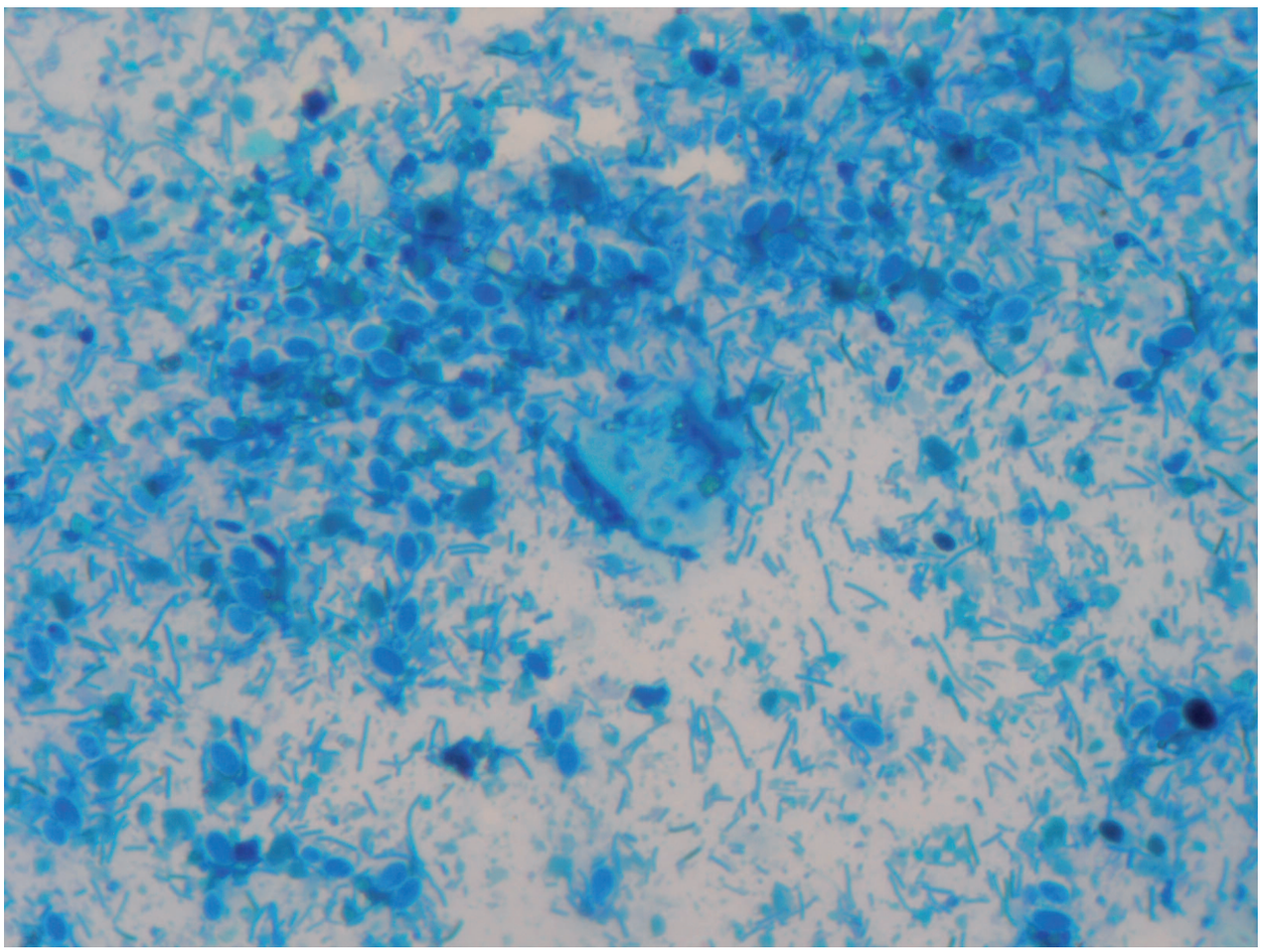

Fig. 1. Direct smear from faeces sample of pigeon suffering from diarrhea. Among abundant intestinal microorganisms many typical fungal yeast-like cells (magnification 1000×, Gram staining).

percentages of fungal organisms at the phylum, class, order, family, and genus levels between the healthy and diseased dogs. The Ascomycota was found to be the most abundant fungal phylum in both healthy and diseased dogs, with the Basidiomycota as the second most abundant. Within the Basidiomycota, the predominant classes were the Agaricomycetes and Ustilaginomycetes, consisting of almost exclusively the order Ustilaginales. Using a pan-fungal PCR, Suchodolski [35] found that 60% of healthy dogs and 76% of dogs with chronic enteropathies were positive for fungal DNA in small intestinal brush samples.

A study of fungi in faecal samples from healthy individuals based on deep sequencing of the ITS1 region identified 66 fungal genera, with 13 additional taxa for which a genus-level classification was not possible. An estimated 184 species were present in total. *Saccharomyces*, *Candida* and *Cladosporium* were the most prevalent. The research was not able to determine whether certain taxa were resident fungal mycobiota or were only transient as part of the dietary intake.

Similar to the relationship between other microorganisms and the host, it has been proposed that a cross-talk exists between opportunistic fungi and the host by the metabolites of the microbiota. In an study of correlations between fungal and bacterial taxa in the gut microbiota, Hoffmann et al. [5] showed that *Candida* and *Saccharomyces* were positively associated with the archea *Methanobrevibacter* and the bacterium *Prevotella*. This group of organisms was most abundant among individuals with high carbohydrate diets, while individuals with diets rich in amino acids and fatty acids had lower levels of *Candida*. The researchers suggest that *Candida*, *Prevotella*, *Ruminococcus*, and *Methanobrevibacter* may form a syntrophic consortium. *Candida* is allows the metabolism of complex carbohydrates, whereas *Prevotella* and *Ruminococcus* ferment the more simple sugars produced by *Candida*. *Methanobrevibacter* may use the products of bacterial fermentation to produce methane and carbon dioxide.

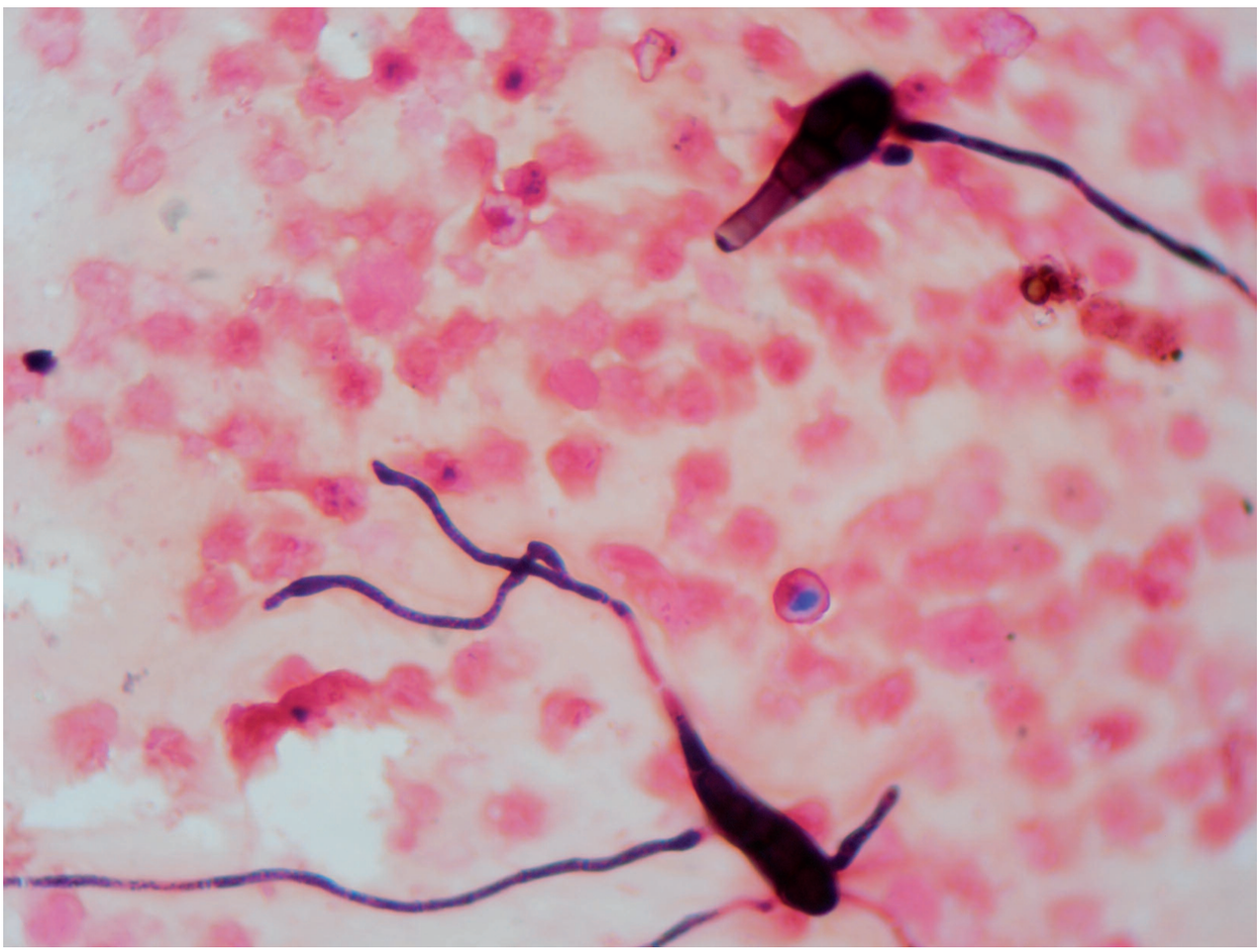

Fig. 2. Direct smear from horse trachea washes sample. Visible typical prolifering fungal cells (magnification 1000×, Gram staining).

Mutualism between fungi and humans is generally not well understood but several examples related to the gut microbiome provide evidence of a beneficial relationship. The yeast *S. boulardii*, closely related to *Saccharomyces cerevisiae*, has been studied for the prevention and inhibition of antibiotic-associated diarrhoea caused by *Clostridium difficile*. Recently, *S. boulardii* has been shown to stimulate IgA production against the *C. difficile* toxin and stimulate gut anti-inflammatory pathways [36]. There is an inverse relationship between *Candida* and *C. difficile*. These studies confirm the ability of fungi to compete with pathogenic organisms by modifying intestinal function and inhibiting inflammatory reactions in bowel diseases such as Crohn's disease and ulcerative colitis [25,37,38].

Respiratory tract

The respiratory tract represents the major entry point for microorganisms, such as airborne viruses, bacteria, and fungal spores. Microorganisms are also subsequently removed by coughing, sneezing, and swallowing. However, if the respiratory tract epithelium becomes damaged, as in the case of *bronchitis* or pneumonia, the host may become susceptible to infection by pathogens descending from the nasopharynx (Fig. 2).

Recent studies suggest that the respiratory tree is not sterile [2,19,40]. Even the lower respiratory tract has a complex dynamic microbiome that is altered during diseases such as cystic fibrosis and chronic obstructive pulmonary disease, but little data exists about the fungal mycobiota of the lungs, with the exception of *Pneumocystis* spp. New molecular surveys suggest that *Pneumocystis* is carried at low levels, even in healthy individuals

In a recent study by Charlson et al. [39], the fungal microbiota of the lungs in selected healthy and lung transplant recipients was analyzed by ITS-based pyrosequencing. The bronchoalveolar lavage from lung transplant recipients showed detectable *Candida* spp., *Aspergillus* spp., or *Cryptococcus*

spp., but fungal colonization was found to be extremely low in the lungs.

Numerous studies have indicated that Th17 cells and cytokine IL-17A are critical to the immune response against various airway infections by microorganisms including fungi. Also, neutrophils release their genomic DNA into the extracellular environment in the form of neutrophil extracellular traps (NETs) and catch the invading pathogens. NETs were found to be induced by opportunistic fungi such as *C. albicans.* It was demonstrated that NETs interact with yeast in both the single-cell form as well as the multicellular hyphal form. In contrast to the protective immune response of Th1 and Th17 cells, Th2 effector cells are considered to have a negative influence in the lung during fungal infections partially because they depress the protective Th1-cell responses. In response to *Candida albicans*, a tryptophan catabolic pathway is exploited by commensal *Lactobacillus* sp. and the mammalian host to induce resistance and stimulate antifungal immunity in the mucosal membrane [2,19,40]

Other example of mycobiota

The spread of the dangerous amphibian fungal chytrid disease in animal hosts, mainly frogs, remains unclear. *Batrachochytrium dendrobatidis*, also known as *Bd*, is a fungus that causes chytridiomycosis. The disease has devastated amphibian populations around the world. However, some amphibian species appear to have an innate capacity to withstand chytridiomycosis infection, and even within species that generally succumb, some populations survive. The ability of some frog species to coexist with the fungus *Batrachochytrium dendrobatidis* may be due to the expression of antimicrobial skin peptides and the presence of symbiotic microbes that benefit from the host by resisting pathogen colonization or inhibiting fungal growth. It seemed that commensal bacteria are resistant to high concentrations of antimicrobial skin peptides [41].

Conclusions

The findings described above suggest that the metagenomic and metabonomic study of microbiota, is affording a new look into the regulation of host immune responsiveness to fungi and mycoses. It appears that fungal diversity should be greater in more severe cases of a disease. The pathogenesis of many single fungal infections has been well described, but the correlation between the whole mycobiome and disease progression remains not fully understood. Fungi cooperate within complex microbial communities to contribute to energy harvest and metabolic homeostasis. Even fungi which are relatively rare within the microbiome may establish roles in immune stimulation. Disruptions within the microbiome interact with the innate and adaptive immune system as part of the holobiome. Nevertheless, fungi are important part of the microbiome, either as a cofactor in disease or as potential pathogens. The mycobiome, both as a whole or its individual members, may play a beneficial role and can act as important preventive and therapeutic agents; for example, *Saccharomyces boulardii* can be used to treat diarrhoeal diseases [12]. It is still unclear why commensal fungi such as *Malassezia* spp. and some *Candida* may change their relationship with the host to a more pathological one and enable disease progression, and it is unknown how the heterogenity of the mycobiome and genetic polymorphisms across human populations may generate various risks for mycobiome-associated diseases.

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