Received: 19 May 2023 | Revised: 6 December 2023 | Accepted: 7 December 2023

DOI: 10.1002/wsbm.1639

ADVANCED REVIEW

WIREs MECHANISMS OF DISEASE WILEY

The yeast–human coevolution: Fungal transition from passengers, colonizers, and invaders

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Funding information
JPI HDHL-INTIMIC, Grant/Award Number: JTC-2017-7; Joint Programming Initiative A healthy diet for a healthy life, Grant/Award Number: 529051018; Regione Toscana, Grant/Award Number: G84I18000160002; Italian Ministry of Agriculture, Food, and Forestry Policies (MiPAAF), Grant/Award Number: DM 36954/7303/18

Edited by: Emily Frieben, Executive Editor

Abstract

Fungi are the cause of more than a billion infections in humans every year, although their interactions with the host are still neglected compared to bacteria. Major systemic fungal infections are very unusual in the healthy population, due to the long history of coevolution with the human host. Humans are routinely exposed to environmental fungi and can host a commensal mycobiota, which is increasingly considered as a key player in health and disease. Here, we review the current knowledge on host-fungi coevolution and the factors that regulate their interaction. On one hand, fungi have learned to survive and inhabit the host organisms as a natural ecosystem, on the other hand, the host immune system finely tunes the response toward fungi. In turn, recognition of fungi as commensals or pathogens regulates the host immune balance in health and disease. In the human gut ecosystem, yeasts provide a fingerprint of the transient microbiota. Their status as passengers or colonizers is related to the integrity of the gut barrier and the risk of multiple disorders. Thus, the study of this less known component of the microbiota could unravel the rules of the transition from passengers to colonizers and invaders, as well as their dependence on the innate component of the host's immune response.

This article is categorized under:
Infectious Diseases > Environmental Factors
Immune System Diseases > Environmental Factors
Infectious Diseases > Molecular and Cellular Physiology

KEYWORDS
fungal evolution, host immunity, host–fungi interaction, mycobiota, trained immunity

1 | INTRODUCTION

Fungi and mammals share a long history of coevolution that has led to the establishment of several different types of relationships (Casadevall, 2012). Exposure to fungi is constant thanks to the environment and diet, which are the main

sources (Fiers et al., 2019). Fungi, and especially *Ascomycota* yeasts, have learned to survive in host organisms, including humans. Their characterization, role, and functional contribution, as part of the human microbiota, have been undervalued for decades, since bacteria numerically outweigh fungi and molecular techniques are not yet able to properly identify the fungal richness in the complex microbial community inhabiting the human host ("Stop Neglecting Fungi," 2017). Furthermore, it was always believed that major systemic fungal infections are rare in the healthy population (Kwon-Chung & Bennett, 1992). Currently, there is not a scientific consensus on the existence of a proper core fungal community (or mycobiota) that stably colonizes the human microbiota (Sharon et al., 2022).

Although the sources and the stability of fungal communities within human microbiota are still a matter of debate, they represent one of the largest eukaryotic kingdoms including opportunistic species that can display pathogenic behaviors especially in non-immune competent hosts (Fisher et al., 2020). The balance between commensalism and pathogenicity relies not only on the genetic features evolved by fungi, but also on the several interactions with the host immune system. Since each fungal cell exposes a surface area to the host that is typically 100 times larger than a bacterial cell, their importance in interacting with the host immune system should not be understated (Naglik et al., 2017; Patin et al., 2019). This evidence, together with insights on deleterious effects of fungi in dysbiosis (Iliev & Leonardi, 2017) and in diseases onset (Köhler et al., 2017), as well as the poorly investigated beneficial role toward host immunity (Jiang et al., 2017; Rizzetto et al., 2010, 2016), suggest that fungi play a fundamental role in the relationships with the human holobiont (Lai et al., 2019). Overall, given these interactions, the human immune system has evolved a fine-tuned mechanism to respond to fungi and tolerate them, discerning self from non-self through the detection of fungal cell components by the innate immune system, followed by a cascade of signaling pathways that leads to activation of gene expression and, ultimately, giving rise to adaptive immunity (Romani, 2011).

In this review, we introduce: (i) the possible evolutionary mechanisms subtending the fungi–host relationships; (ii) the multiple relationships between fungi and human hosts; and (iii) the mechanisms of recognition of fungi by the host immune system and their transition as passengers, invaders, and colonizers.

2 | HOST–FUNGI COEVOLUTION

Since fungi diverged from animals, about 1 billion years ago (Hedges et al., 2004; J. W. Taylor & Berbee, 2006), they have become one of the most important sources of genetic diversity on Earth (Peay et al., 2016; Wainright et al., 1993). Moreover, they coevolved with animals as part of holobiont ecosystems. Fungi could establish different types of relationships with the host, ranging from mutual to commensal and parasitic/pathogenic interactions, (Gnat et al., 2021; Seyedmousavi et al., 2018).

Nonetheless, fungi are drastically understudied, such that they have been referred to as the "hidden kingdom" (Fisher et al., 2020). Only in the last 5 years, several research groups have raised the attention on the urge to deepen the knowledge about fungal biology in order to tackle the threats coming from emerging pathogens (Fisher et al., 2016; "Stop Neglecting Fungi," 2017). One of the reasons why this kingdom has been historically understudied could be the fact that humans, and mammals in general, are biologically less prone to lethal fungal infections with respect to other classes of animals (Canny & Gamble, 2003; Connole et al., 2000; Kwon-Chung & Bennett, 1992; Pollock, 2003). Until the middle of the last century, systemic diseases in humans were considered rare and nowadays they usually do not occur unless in cases of impaired immune function, exposure to large inocula, use of immunosuppressive drugs, integument compromise by catheters and surgery and disruption of the microbiota and dysbiosis (Deshaw & Pirofski, 1995; Edwards, 1991; Fessel, 1993; Fisher et al., 2000; Gupta & Kogan, 2004; J. I. Ward et al., 1979).

The relatively low abundance of diseases caused by fungi, despite their ubiquitous presence in every environment, suggests that mammals were evolutionarily selected to defend themselves against these microorganisms. Specifically, evidence suggests that the most important characteristics of mammals for avoiding lethal fungal infections are the combination of a high basal temperature and an advanced immune system (Kwon-Chung & Bennett, 1992). In contrast, fungal diseases have a greater impact in terms of frequency and lethality for a huge variety of ectothermic animals (Berger et al., 1998; Daszak et al., 1999; Fisher et al., 2012), while mammals can succumb to usually non-lethal fungal infections when they take place in cooler body sites or at a cooler time of the year (Blehert et al., 2009; Perfect et al., 1980). The importance of host–fungi interactions in balancing the rates and causes of mortality among different classes in the animal kingdom has been stressed to the point that an evolutionary hypothesis concerning the emergence of mammals over reptiles at the Cretaceous–Paleogene (K–Pg) boundary (formerly known as the Cretaceous–Tertiary boundary) was proposed (Casadevall, 2005), discussed (Casadevall, 2012), and recently revisited (Casadevall & Damman, 2020). In that era, an

asteroid impact (Schulte et al., 2010) triggered a mass extinction, followed by deforestation (Vajda et al., 2001) and an ubiquitous fungal bloom (Vajda & McLoughlin, 2004). The up-to-date hypothesis, called "fungal infection-mammalian selection" (FIMS) by Casadevall and Damman (2020), states that, despite their more energetically expensive bodies and lifestyle, mammals survived the catastrophe better than reptiles because their endothermy would have protected them from fungal diseases. In contrast, the rapid global cooling would have negatively selected ectothermic animals in terms of reproduction and sustenance, as well as deadly fungal infections that proliferate at low temperatures. In this scenario, mammals began to dominate the current Cenozoic era, together with the ubiquity of microorganisms, including fungi. Since several different types of stable relationships between mammals (in particular humans) and fungi are known, it is reasonable to infer that both groups have evolved in a way that, on one hand, enabled fungi to survive in the hostile mammal microbiota environment and, on the other hand, enabled mammals to tolerate their presence, both as commensal and opportunistic dwellers. A graphic illustration of the FIMS theory is depicted in Figure 1.

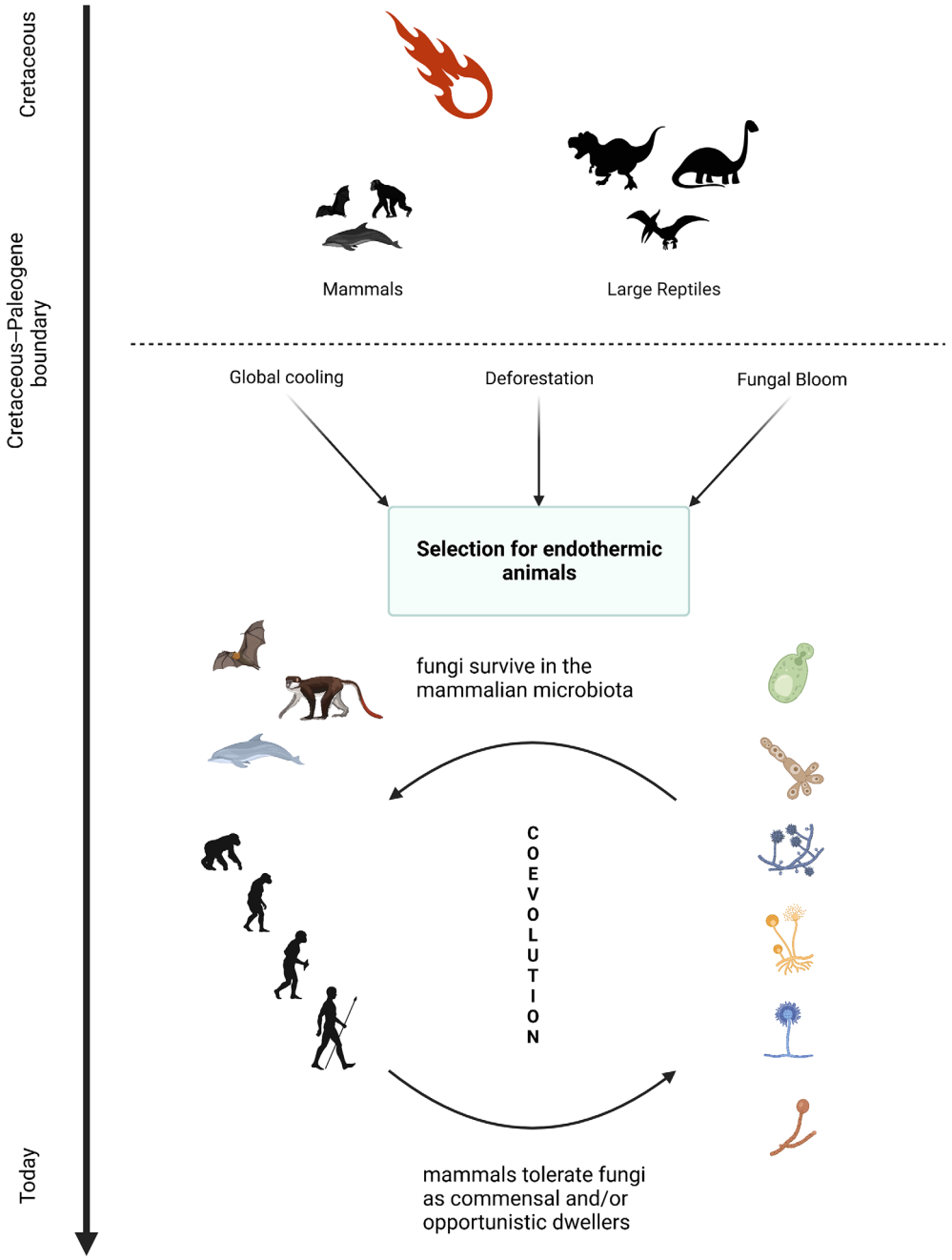

FIGURE 1 Representation of "fungal infection-mammalian selection" (FIMS) evolutionary theory as formulated by Casadevall and Damman (2020).

2.1 | Fungi: Transients or colonizers?

Some authors have attempted to discern between what is considered the core mycobiota and a transient fungal colonization that most likely comes from environmental species. Currently, there is still not sufficient evidence of the existence of a core mycobiota in each human body district (Sharon et al., 2022). The observed interindividual and intraindividual variability of the mycobiota could suggest a high functional redundancy among fungal residents or could be due to technical artifacts arising from the low absolute abundance of fungi compared to bacteria.

A small-scale study by Auchtung et al. (2018) sought to identify a possible core mycobiota of the human gastrointestinal (GI) tract analyzing stool samples of healthy volunteers. For their investigation, the authors considered that, in other studies on mycobiota, low longitudinal stability across samples from a single individual was recurrent and that most commonly detected fungal genera are also present in food and the oral cavity (Ghannoum et al., 2010; Hallen-Adams & Suhr, 2017; Oh et al., 2014). Since the alleged core gut mycobiota could be obscured in metagenomic analysis from diet-related fungi, the authors conducted an experiment where volunteers of diverse geographical areas and with different dietary habits followed four controlled diets as representative of major food groups and relatively low fungal load. An extremely low fungal abundance was found compared to the bacterial community (from 0.001% to 0.01%). *Candida albicans* and *Saccharomyces* were the unique Ascomycetes yeasts present in each sample. Furthermore, following a *Saccharomyces cerevisiae*-free diet, the *Saccharomyces* operational taxonomic unit dropped below the limit of detection within a few days. Moreover, they tried to verify whether *Candida* species found in the human gut derive from the swallowing of saliva. They observed that when a healthy adult volunteer increased the frequency of cleaning of teeth, the abundance of *C. albicans* in stool was lowered 10- to 100-fold. Therefore, the authors concluded that in healthy adults of Western society there are few or no fungal species that colonize the GI tract.

Conversely, a more recent study by van Tilburg Bernardes et al. (2020) sought to determine the role of colonizing fungi using a gnotobiotic mouse model. Results showed that, in the absence of bacteria, fungi can be cultivated from fecal samples several weeks after initial inoculation. The authors concluded that fungi are gut dwellers and that they do not require bacterial communities to engraft in the mouse gut. Moreover, when bacteria and fungi coexist, the fungal concentration is lower, but the fungal community is rich, revealing not only interkingdom competition or antagonism but also beneficial relationships.

Other studies focused on specific body sites to assess the nature of human mycobiota. Kramer et al. (2015) showed that the mycobiota of the upper respiratory tract was dominated by transient species, and that there is not enough scientific evidence to distinguish between resident and transient components of airway mycobiota.

Regarding oral mycobiota, there are indications of both resident and transient fungi (Santus et al., 2021). Ascomycetes yeasts of *Candida* and *Saccharomyces* genera have been found in several studies, but only *Candida* is recognized to date as an active colonizer of the mouth, especially *C. albicans* that has been identified in both culture-dependent and -independent studies (Monteiro-da-Silva et al., 2014; Zaura et al., 2009).

As far as the gut mycobiota is concerned, studies in mice and humans showed that the gut ecosystem could be populated by both a transient, and a resident community of fungi (Santus et al., 2021). The Human Microbiome Project data showed that the most abundant Ascomycetes yeasts are *Saccharomyces* (Fröhlich-Wyder et al., 2019; Heitmann et al., 2018; Nielsen, 2019; Shankar, 2021), *Candida* and *Cyberlindnera* (Buerth et al., 2016). These genera are components of several fermented food and beverages, such as *Saccharomyces*, or food additives, such as *Cyberlindnera* (Nash et al., 2017). As already mentioned, *Candida* is the most abundant fungal genus of oral mycobiota, and almost certainly the main colonizers of several human body districts, including the gut ecosystem.

In general, the scientific consensus agrees on the fact that the great intraindividual and interindividual variability observed in the human gut mycobiota (Human Microbiome Project Consortium, 2012) suggests that the most representative fungal genera could be introduced through food since fungi are usually present in most of the human diets and fermented foods (Fiers et al., 2019; Graves & Hesseltine, 1966; Raimondi et al., 2019; Tournas & Niazi, 2018). However, studies on in vivo mouse models through a culture-independent approach (Aykut et al., 2019; Heisel et al., 2017; Qiu et al., 2015; Rosshart et al., 2019; Scupham et al., 2006; Yeung et al., 2020) showed a different scenario. On one hand, *Candida* and *Saccharomyces* genera were found in mouse feces but not in chow, and on the other hand, their abundance was a lot higher in the feces, or a high percentage (80%–90%) of the taxa identified in the feces were not present in chow (Heisel et al., 2017; Iliev et al., 2012; Qiu et al., 2015; Scupham et al., 2006).

Altogether, these studies suggest that the investigation of the core gut mycobiota needs to be further deepened. The discrepancies found can almost certainly be attributed to the different models used (human and mouse), to the culture-

dependent or culture-independent approaches, or to not yet perfected sequencing analysis methods. Figure 2 shows a schematic representation of the different forms of human–fungi interactions.

2.2 | Fungal evolution toward pathogenesis

Within the large number of identified fungal species, only a few are known to be true pathogens, although it is becoming evident that probably some fungi (included the harmless ones, such as *S. cerevisiae*) can be opportunistic or accidentally pathogens in the presence of a non-immune competent host. Pathogenicity has evolved within the fungal kingdom through different mechanisms and genetic variations. Genes associated with fungal pathogenicity show a degree of heterogeneity not only at the species level, but also at the strain level. However, little is known regarding the extent of this variability. Indeed, pathogenic fungi are not a monophyletic group and the characteristics they have developed have probably evolved to survive in conditions independent of successful infection of the human host (Bowman et al., 1996; Rizzetto & Cavalieri, 2011). It has been proposed that the traits associated with pathogenicity are the same ones that have enabled them to survive in nature by adapting to a wide range of even extreme conditions (Casadevall & Pirofski, 2007; Gostinčar et al., 2018). For example, it has been observed that Ascomycetes tend to be more thermotolerant and present in different environments than other fungal phyla. This may explain at least part of the abundance of human pathogens, but also commensals, within *Ascomycota* (Robert et al., 2015; Rokas, 2022). However, fungal adaptive strategies within the human host may diverge from their natural habitat. This is evident when comparing *S. cerevisiae* natural and clinical strains, the latter show increased levels of heterozygosity and pseudohyphal development and a reduction of sexual reproduction (Magwene et al., 2011; Strope et al., 2015). These microorganisms have developed pathogenicity as a consequence of complex interactions between themselves, their host, and the environment (Casadevall, 2017). The use of an ecological-evolutionary approach, coupled with recent technological innovations, is currently making it possible to understand and deepen the mechanisms underlying fungal pathogenicity. To be able to infect humans, fungi must have four characteristics: human body temperature resistance (e.g. fever, >37°C), avoidance or breakthrough of surface barriers, tissue lysis and penetration, and immune defense resistance (Köhler et al., 2017). These conditions are only met by a small number of species which differ considerably in terms of adaptation to pathogenicity.

In the context of Ascomycetes yeasts, *Candida* genus include the most prevalent human commensals. However, this genus also includes the most common human pathogens, such as *C. albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei*, and the emerging *Candida auris*. These species are responsible for a large number of diseases, ranging from minor mucosal infection, such as vulvocandidiasis and oropharyngeal thrush to potentially fatal diseases, including disseminated hematogenous and invasive candidiasis (Pfaller & Diekema, 2007). Thanks to its major ability of adaptation to human host, *C. albicans* is the dominant species among commensals and pathogens

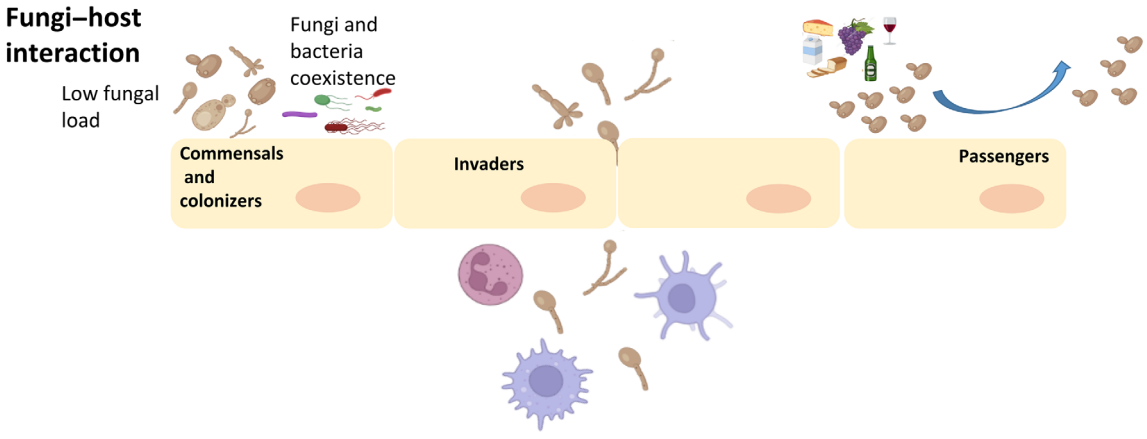

FIGURE 2 Interaction between fungi and human hosts. Three scenarios are represented in the gut environment: (i) commensal fungi and bacteria coexist and can persist into the gut ecosystem as colonizers; (ii) opportunistic or accidental fungal pathogens can invade the gut barrier. Here, the host immune response is ready to trigger an appropriate immune response to fight the invaders and to maintain homeostasis; (iii) food-borne and environmental fungi can be transient microorganisms and leave the human body.

accounting for almost half of disseminated illness and an even higher proportion of mucosal infections. Its pathogenicity is mainly linked to morphological plasticity that enables it to reversibly switch from yeast to hyphal growth (Chow et al., 2021). Recently, the chromatin-mediated epigenetic regulation of this switching mechanism has been reported by Iracane et al. (2021) that highlight the role of environmental stimuli in triggering pathogenic behavior. It is interesting to note that cryptic species, such as *C. albicans* and *Candida dubliniensis*, even though they share several phenotypic traits and do not have major disparities in the gene content (Jackson et al., 2009), are quite different in terms of virulence. However, looking at orthologous genes' expression levels, a systematic comparison highlighted main differences in 15 genes involved in glycolysis that are less expressed in *C. dubliniensis*. In the same study (Singh-Babak et al., 2021), after genetically engineering *C. dubliniensis* to overexpress these genes, an increase in virulence of the species was observed. Thus, recent evidence shows both gene variation and regulation of expression levels are mechanisms capable of inducing and modulating pathogenicity in fungi. As previously mentioned, temperature is a selective pressure factor to which fungi are able to respond promptly. It has been assumed that current climate change, and the consequent global warming, are selecting thermotolerant fungi able to become human pathogens (Garcia-Solache & Casadevall, 2010; Nnadi & Carter, 2021). This is the case of the recently discovered *C. auris*, which has an environmental reservoir (Arora et al., 2021). This species has caused simultaneous nosocomial infections in more than 30 countries in the last 10 years, probably representing the first pathogen selected by global warming (Casadevall et al., 2021). With the same mechanism, in the last three decades also *C. glabrata* infections have become more frequent (Gabaldón & Carreté, 2016), thanks to its ability to tolerate temperatures superior to 37°C, to withstand various types of stress including prolonged starvation and to have great adherence to host tissue. Nevertheless, from an evolutionary point of view, this species represents an outlier since it is more linked to *S. cerevisiae* than to other *Candida* species. These two species in fact belong to the same Saccharomycetaceae clade which is characterized using the classic genetic code (Mühlhausen & Kollmar, 2014)—in contrast to the *Candida* CTG clade, in which CUG encodes the amino acid serine instead of leucine (Santos et al., 2011) and both have a duplicated genome as a result of the inheritance of an ancient common ancestor (Wolfe & Shields, 1997). Along with *C. glabrata*, *C. krusei* is the other clinically isolated species not included in the CTG clade, but little is known about the virulence mechanisms of this species, although the number of nosocomial infections has increased in recent years (Gómez-Gaviria & Mora-Montes, 2020). To date, it is well known that there are important physiological differences between *C. glabrata* and *C. albicans* since they do not even share a large number of protein-coding genes. It has been noticed that even in the case in which they share some orthologous genes, the functional divergence may be of such magnitude that it leads to completely different outcomes in terms of virulence, as reported for instance by MacCallum et al. (2006). Null mutations in the transcription factor ACE2 result in reduced virulence in *C. albicans* and increased virulence in *C. glabrata*. However, *C. glabrata* ability to reshape its metabolism in response to phagocytosis is a similar characteristic known for *C. albicans* (Kaur et al., 2007). In contrast, its closest relative, *S. cerevisiae*, does not appear to be able to provide as robust a response (Lorenz et al., 2004).

S. cerevisiae has long been considered a non-pathogenic microorganism. However, a comparison of environmental and clinical strains showed that the latter are mosaic strains characterized by heterogeneous gene content due to outcrossing between different subpopulations (Cavalieri, 2010; Magwene, 2014). Clinical strains in fact generally show a reduced capacity for sexual reproduction, increased pseudohyphal development and copper resistance (Strope et al., 2015). Since *S. cerevisiae* lacks homologous genes for adhesin and shows lower adhesion levels to human tissue compared to *Candida* species, it has been proposed that it can behave like an opportunistic pathogen only when host barriers integrity has been formerly compromised (Pérez-Torrado et al., 2015).

Due to the increasing number of immunocompromised individuals and as a consequence of climate change and globalization, we are witnessing a progressive increase in the number of emerging pathogenic fungi. It therefore becomes crucial to understand the ecology and evolutionary history of these microorganisms in order to systematically classify them. A better understanding of the molecular mechanisms underlying fungal pathogenicity and virulence could make it possible not only to predict the emergence of new pathogens, but also to develop targeted therapies.

3 | FUNGI AND THE HOST IMMUNE SYSTEM

Healthy populations live surrounded by environmental fungi and harbor a rich mycobiota without frequently incurring harmful infections. This is possible thanks to a strong immune system that has evolved to respond to fungi and tolerate them. Since fungi are ubiquitous and range across several mechanisms of interactions with other microorganisms, nearly all immunity types of the host are involved in the process of achieving balance with the fungal community.

Immune homeostasis is exerted on barrier surfaces, such as mucous membranes, and constantly shapes immunity. A proper immune response relies on the host's ability to discern self from non-self, starting with the detection of fungal cell components by the innate immune system, followed by a cascade of signaling pathways that leads to the activation of gene expression and, ultimately, giving rise to adaptive immunity (Figure 3). Although mycobiota have been neglected for a long time, in the last 10 years numerous studies have focused on the impact of fungal species on the host immune system and vice versa (Cui et al., 2013; Hohl, 2014; Iliev & Leonardi, 2017; Lai et al., 2019; Lionakis et al., 2017; Netea et al., 2015; Rizzetto et al., 2014; Romani, 2011; Santus et al., 2021; Underhill & Iliev, 2014; Underhill & Pearlman, 2015; Wheeler et al., 2017; X. Zhang et al., 2020). These comprehensive reviews deepen all aspects of the immunological response toward fungal communities, and therefore the following subsections will provide a brief overview of the current knowledge, focusing on the most important features that allow human bodies to both tolerate and control the mycobiota.

3.1 | Fungal recognition by host immune system

The response to fungi begins with their recognition by innate immunity, followed by downstream signaling pathways that drive innate, adaptive, and humoral responses. In particular, fungi are recognized by host immune cells' pattern recognition receptors (PRRs) that sense pathogen-associated molecular patterns (PAMPs) of fungi (Figure 3a). Fungal PAMPs are mostly components of the cell wall, such as glucans, mannans, and the chitin monomer *N*-acetylglucosamine (Doering, 2009; Erwig & Gow, 2016; Hatinguais et al., 2020; Lee & Sheppard, 2016; Netea et al., 2008). The most important PRRs that can identify fungi are Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), and galectin-3, extensively reviewed elsewhere (Iliev & Leonardi, 2017; Romani, 2011; Underhill & Pearlman, 2015; Wheeler et al., 2017; X. Zhang et al., 2020). Through differential recognition by several types of PRRs, the immune system can discriminate between commensal, passenger, opportunistic, and pathogenic fungi in order to orchestrate a proper reaction and maintain homeostasis between all the microbial populations. The importance of PRRs in immune homeostasis is underlined by the effects of mutations in these receptors, which lead to increased infections, tissue burden, and exacerbated inflammation (Ifrim et al., 2015, p. 201; Iliev et al., 2012; Netea et al., 2002). Among PRRs, CLRs such as dectin-1, dectin-2, dectin-3, macrophage inducible Ca_2^+-dependent lectin receptor (Mincle), and the mannose receptor likely play the most central role in fungal recognition, activating several pathways, including the Syk-Card9 pathway, which leads to different signaling cascades and an inflammatory reaction (Brown & Gordon, 2003; Dambuza & Brown, 2015; Drummond & Brown, 2013; Geijtenbeek & Gringhuis, 2009; Plato et al., 2015; Sancho & Reis e Sousa, 2012; Smeekens et al., 2014; P. R. Taylor et al., 2007). Also, TLRs are essential parts of fungal sensing, specifically TLR2 and TLR4 for cell wall components, whereas TL3, TLR7, and TLR9 (which are expressed intracellularly) for exogenous RNA and DNA (Bourgeois & Kuchler, 2012; Elieh Ali Komi et al., 2018). Sensitivity to fungal infections is strongly influenced by mutations in both *CLR* (Gross et al., 2006; Saijo et al., 2007; P. R. Taylor et al., 2007; Whitney et al., 2014) and *TLR* genes (Bochud et al., 2008; Carvalho et al., 2008; Netea et al., 2002). Although fungal NLR ligands are not fully defined yet, the NLRP3 inflammasome process has been shown to influence the defense against mycobiota (Gross et al., 2009). PRRs on immune cells initiate downstream intracellular events that eventually lead to the clearance or tolerance of fungal cells within the body (Figure 3b). The choice between innate or adaptive immune response depends on the cell type involved (Patin et al., 2019). In addition, humoral immune mechanisms, such as the complement and specific antibodies against fungi, play an important role in antifungal immunity (Casadevall & Pirofski, 2012; Netea et al., 2015; Speth et al., 2008).

3.2 | Innate response

An innate immune response is the first essential step for fungal clearance and the initiation of adaptive responses through cell–cell crosstalk. Several studies deeply reviewed all the known aspects of this defense mechanism (Dambuza et al., 2017; Drummond et al., 2014; Salazar & Brown, 2018; Underhill & Pearlman, 2015). Therefore, here we will provide a brief overview in order to summarize the most important features regarding the factors that drive the shift between innate and adaptive responses (Figure 3b). Among all immune cells, neutrophils are shown to be the most effective in fungal clearance for their ability in killing them through oxidative bursts after phagocytosis or through NETs, secrete antifungal molecules and prevent yeast to hyphal transition (Branzk et al., 2014; Brown, 2011; Ermert

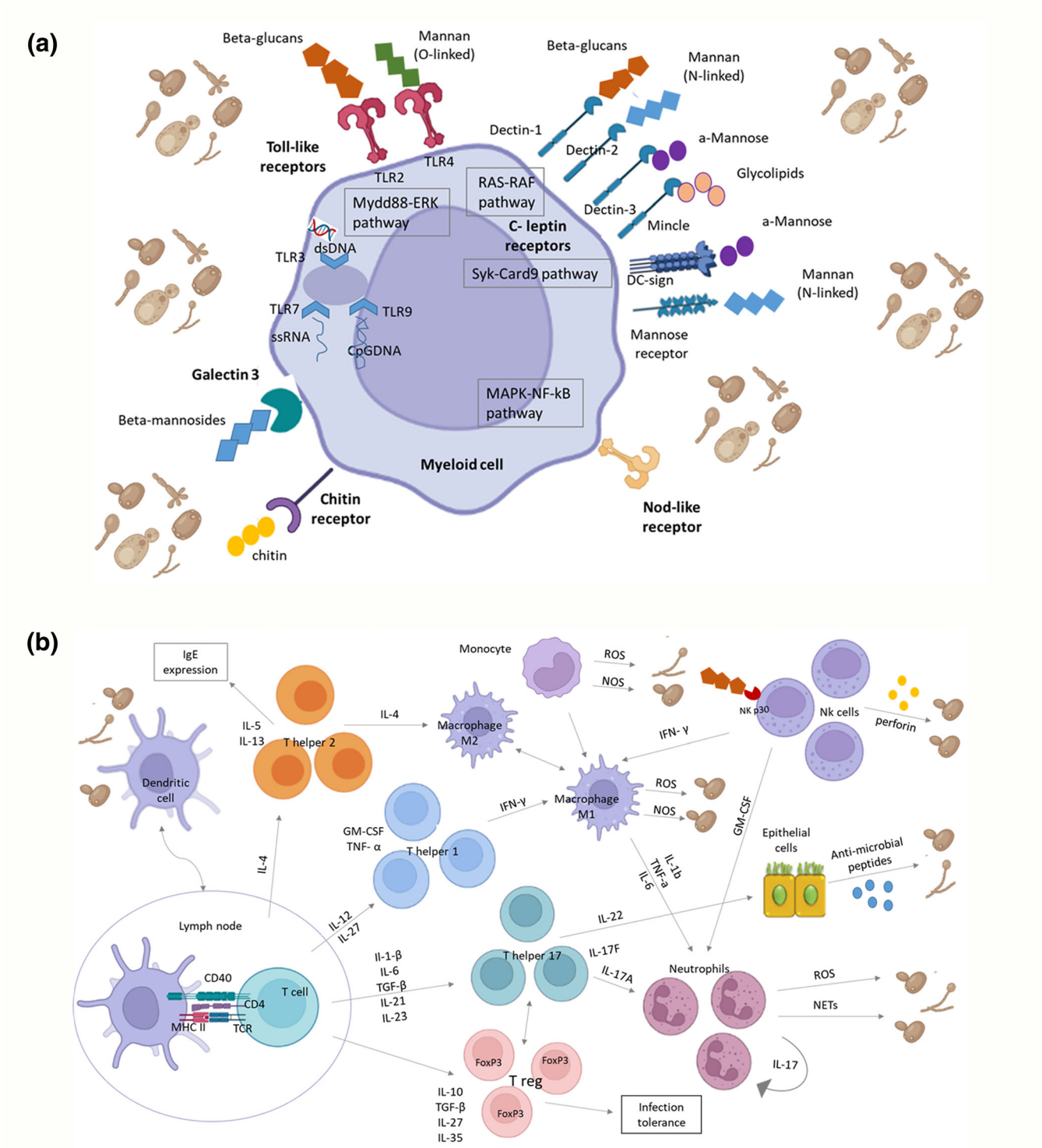

FIGURE 3 Fungi and the host immune system. (a) Schematic representation of fungal recognition mechanisms by innate immunity. The principal pattern recognition receptors (PPRs) and the pathogen-associated molecular patterns (PAMPs), mainly of the fungal cell wall, are reported. (b) Schematic representation of fungal recognition mechanisms by innate and adaptive immunity. An innate immune response is the first essential step for fungal clearance. Neutrophils and natural killer (NK) cells are able to kill fungi through different mechanisms, including oxidative bursts after phagocytosis or through neutrophil extracellular traps (NETs), secretion of antifungal molecules that prevent yeast to hyphal transition, and the initiation of adaptive responses. Also, monocytes and macrophages can kill fungi, although less efficiently than neutrophils and NK cells. Dendritic cells (DCs), after exposure with fungal PAMPs, module cytokines production, as well as activation markers, migrating to lymph nodes and priming T cells to initiate an adaptive response.

et al., 2013; Missall et al., 2004; Urban et al., 2009; Warnatsch et al., 2017; Wozniok et al., 2008), and also the most crucial because of the increased risk of invasive fungal infections due to neutropenia (Koh et al., 2008; Uzun et al., 2001) or mutations in genes associated with neutrophil activity (Lehrer & Cline, 1969; Swamydas et al., 2016; Winkelstein et al., 2000). Also, monocytes and macrophages can kill fungi, even if less effectively than neutrophils (Hünniger et al., 2014). They exert an important antifungal activity in peripheral organs (Ngo et al., 2014) and fungal infections are enhanced after their depletion (Qian et al., 1994) or mutations involving the chemokine receptor CX3CR1 (Lionakis et al., 2013; Lionakis & Levitz, 2018). Other major contributors to the immune response to fungi come from epithelial cells, which release antimicrobial peptides (AMPs) and represent the first barrier for environmental fungi (Kolls et al., 2008), natural killer (NK) cells, which are primarily active against hyphal forms trough cytotoxicity (S. S. Li et al., 2013; Mody et al., 2019). They have also been shown to regulate other immune cells through cytokines production (Campbell & Hasegawa, 2013; Schmidt et al., 2017), other innate lymphoid cells (Gladiator et al., 2013; Y. Huang et al., 2015; Mear et al., 2014) and innate-like lymphocytes such as γδ T cells (Albacker et al., 2013; Cohen et al., 2011). Finally, DCs, considered as a bridge between innate and adaptive immunity, play a fundamental role in shaping the proper immune reaction toward fungi (Paul, 2011; Steinman & Hemmi, 2006). After exposure to fungal PAMPs, DC module cytokine production, as well as activation markers, migrating to lymph nodes and priming T cells to initiate an adaptive response (Kashem et al., 2015; Ramirez-Ortiz & Means, 2012; R. M. Roy & Klein, 2012) (Figure 3b). The most studied signaling pathway of immune activation is the "spleen tyrosine kinase - caspase recruitment domain-containing protein 9" (SYK-CARD9), which is downstream of fungal PAMP recognition by CLRs and induce a large range of cytokine gene expression (Geijtenbeek & Gringhuis, 2009; Hardison & Brown, 2012; LeibundGut-Landmann et al., 2007). The organization of innate and adaptive responses to fungi is tuned by the production of cytokines by immune cells, already comprehensively reviewed elsewhere (Becker et al., 2015; Underhill & Pearlman, 2015; R. A. Ward & Vyas, 2020).

3.3 | Adaptive response

The central role of cytokines produced by immune cells after fungal recognition is especially highlighted in the activation of the adaptive immunity, a mechanism that involves primarily DCs, although macrophages could also be part of it. DCs primes naïve CD4+ and CD8+ T cells through fungal antigen presentation and release various panels of cytokines in order to drive the differentiation of T-cell subsets (Iwasaki & Medzhitov, 2010) (Figure 3b). Although CD8+ T cells have been shown to participate in antifungal response (Hernández-Santos et al., 2013; Leibundgut-Landmann et al., 2008; Lindell et al., 2005), especially in case of CD4+ deficiency (Nanjappa et al., 2012), the pivotal role in antifungal adaptive response is played by T-helper cells (Th), which derive from CD4+. Once differentiated, the principal effector function of Th cells is the release of cytokines that allow the host to properly respond to the fungal presence. As well as for the innate form, antifungal adaptive immunity has already been extensively reviewed (Speakman et al., 2020; Verma et al., 2014; Wüthrich et al., 2012), thus here we will summarize the most important Th responses in the context of fungal presence. Th1 immunity is mainly directed toward defense against fungal pathogens through the production of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and granulocyte/monocyte colony-stimulating factor (GM-CSF), which lead to the classical pathway of macrophages activation and antibody class switching to IgG2, as well as the enhancement of phagocytosis and activity of antigen-presenting cells (Beaman, 1987; Novak & Koh, 2013; Schroder et al., 2004; Shalaby et al., 1985; Snapper & Paul, 1987; Subramanian Vignesh et al., 2013). Th2 immunity has shown to be mostly implicated in allergic response to fungi through the production of interleukin (IL)-4, IL-5, and IL-13, which drive an alternative activation to macrophages, and induction of IgE expression, therefore resulting in a detrimental influence on host health during fungal infections (Cenci et al., 1993; Müller et al., 2013; Voelz et al., 2009; Z. Zhang et al., 2017), although a protective role of Th2 cells has been described in *Pneumocystis pneumonia* (Nelson et al., 2011; Perez-Nazario et al., 2013). Similarly, Th9 cells have been associated with enhanced fungal asthma, increased severity of chronic airway hyperreactivity and impairments in gut fungal dissemination and inflammation (Kerzerho et al., 2013; H. Li et al., 2018; Renga et al., 2018). Th17 immunity plays, together with Th1, a central role in fungal response. Th17 differentiation and expansion are prompted by IL-6, IL-21, and IL-23 (Aggarwal et al., 2003; Korn et al., 2007; Nurieva et al., 2007), while both IL-1 and transforming growth factor beta (TGF-β) have been shown to produce controversial effects (Das et al., 2009; Mangan et al., 2006). This T-cell subset is identified by the production of IL-17A, IL-17F, and IL-22, and their antifungal activity is carried out by two main mechanisms: in systemic infections by the recruitment of neutrophils, and in mucosal infections by the induction of AMPs and β-defensins from epithelial

cells and keratinocytes (Conti et al., 2011; De Luca et al., 2010; Hernández-Santos & Gaffen, 2012). Moreover, studies have shown that Th17 cells enhance the production of IgA (Cao et al., 2012; Hirota et al., 2013) and that Th17 cells induced by gut *C. albicans* could become cross-reactive to other fungi in different body districts, indicating that a single member of the mycobiota can elicit a systemic antifungal response, with potential risks for inflammatory and autoimmune diseases (Bacher et al., 2019). Regulatory T cells (Treg), which are composed of different subsets, contribute to an appropriate regulation of the antifungal response in order to limit damage to the host. They exert this role by (i) secretion of inhibitory cytokines such as IL-10, TGF-β, or IL-35, (ii) repression of IL-2 production and (iii) down-modulation of antigen-presenting cells (Goodman et al., 2012). It is still not fully understood how they are generated in response to fungal infections, but some studies have shown that FoxP3+ Tregs promote immune responses against *Candida* in mice (Feng et al., 2011), whereas a fungal stimulation of human peripheral blood mononuclear cells stimulates a Treg but not an effector T-cell response, highlighting the tolerogenic potential of the firsts through an inflammation dampening mechanism (Bacher et al., 2014). Therefore, other studies are required to clarify the role of Tregs in the context of fungal commensalism and pathogenesis. Finally, although early studies concluded that humoral immunity is not necessary for antifungal response (Carrow et al., 1984; Hurd & Drake, 1953; Monga et al., 1979), more recent works showed that immunoglobulins directly target antigens of the fungal cell wall (Casadevall & Pirofski, 2012) and exert a protective immune response both binding to the fungal surface (a role mostly played by IgA) and enhancing the microbicidal potential of effector cells (Brena et al., 2011; Cao et al., 2012; McClelland et al., 2010; Nabavi & Murphy, 1986). Nevertheless, the investigation of B cells during fungal infections is still in its early stages.

3.4 | Immune system adaptive mechanisms: Fungal-mediated immune enhancing and trained immunity

Yeasts resident in the intestinal tract constantly interact with the immune system; however, they do not necessarily represent a threat for the host inducing an inflammatory response. Some studies have better defined the role of yeasts in host–microbe interaction (Di Paola et al., 2020; Hall & Noverr, 2017). The exposure of non-pathogenic yeasts, such as *S. cerevisiae* and *C. albicans*, induces the activation of human monocyte cells causing a Th17-mediated differential response (Rizzetto et al., 2010, 2014). The yeast *C. albicans* is extensively studied for its ability to switch from a commensal to a parasitic microorganism. *C. albicans* is commonly tolerated by the host as a commensal organism as it does not activate innate immune responses that cause inflammation. However, following dysbiosis and/or immune suppression, *C. albicans* can proliferate, inducing hyphae development and thus activating innate immune responses with consequent inflammatory process (Hall & Noverr, 2017). The continuous recruitment of immune cells by *C. albicans* into the vaginal mucosa causes an increased activity of neutrophils, damaging the mucosa and causing symptomatic candidiasis (Bradford & Ravel, 2017; Fidel et al., 2004). The role of *S. cerevisiae* has also been widely discussed since the presence of circulating ASCAs is associated with the incidence of several human chronic inflammatory and autoimmune diseases (Barclay et al., 1992; Kaul et al., 2012; Mankaï et al., 2013; Shor et al., 2012). According to these studies, *S. cerevisiae* shows negative immunogenic activity capable of threatening human health. However, *Saccharomyces boulardii* is used as a probiotic for the treatment of GI disorders showing traits of a mutualistic symbiont (Abid et al., 2022; Szajewska et al., 2016). Given this controversial evidence, the role of yeasts has not been completely resolved yet and probably the immunogenic activity drastically depends on the strain-specific wall structure rather than taxonomic species (Briard et al., 2021; Marakalala et al., 2013).

It is clear that the role of yeasts in the human immune system homeostasis implicates a level of complexity that goes beyond the commensal interaction and that the relationship between commensal yeasts and their human host has crossed several coevolution steps. It has been proposed that trained immunity (Figure 4) represents a mechanism that provides the host an evolutionary advantage. It is defined as a long-term functional modification of innate immune cells which leads to a greater response to a second unrelated immune challenge (Netea et al., 2020) (Figure 4). Trained immunity was initially referred to bacteria only, exerted through lipopolysaccharides recognition (Netea et al., 2011), but also fungi have been shown to participate (Quintin et al., 2012) and its role during mucosal diseases has been recently reviewed (Yu et al., 2022). Systemic infection of mice with a non-pathogenic strain of *C. albicans* PCA-2 conferred protection against subsequent infection with lethal concentrations of the *C. albicans* pathogenic strain CA-6 and/or *Staphylococcus aureus* (Bistoni et al., 1986). These mechanisms were not regulated by the adaptive immune response, but by a T-independent functional reprogramming operated by fungal cell wall β-glucans (Bistoni et al., 1988,

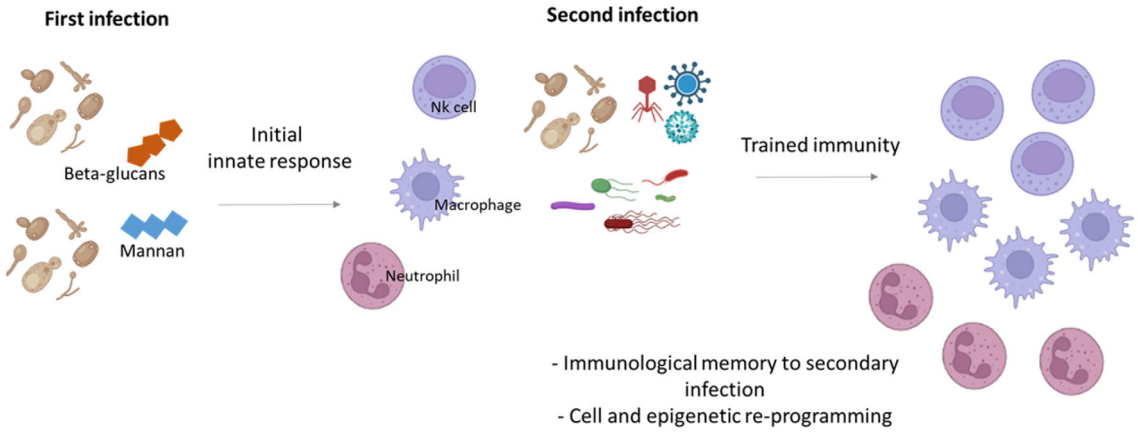

FIGURE 4 Trained immunity induced by fungi. A primary fungal infection (represented by exposure to fungal cell wall components) induces an initial innate immune response. The innate immune cells (natural killers, macrophages, neutrophils) are epigenetically reprogrammed during exposure to microorganisms, allowing an enhanced response upon a second infection by fungi, bacteria, or virus.

p. 88; Quintin et al., 2012). The PCA-2 strain was able to induce increased levels of GM-CSF, TNF-α, IL-1, and IFN-γ in mice model, and these levels persisted for several days after infection (Vecchiarelli et al., 1989).

S. cerevisiae has been proven to induce trained immunity in human monocytes in a strain-dependent manner, resulting in increased production of TNF-α and IL-6 upon secondary stimulation with TLRs ligands. Moreover, the differential activation of the immune system strictly depends on the strain used due to the different chitin content of the cell wall (Rizzetto et al., 2016). Dectin-1 was depicted as a target receptor involved in the fungal wall, through recognition of β-glucans (Moerings et al., 2021; Walachowski et al., 2017). Exposure of mice lacking functional T and B lymphocytes to *C. albicans* and fungal cell wall β-glucans resulted in protection against *C. albicans* reinfection through a process that directly involved the Dectin-1 receptor pathway and the Raf-1 mediator leading to histone H3K4 trimethylation resulting in a functional epigenetic reassortment of monocytes (Quintin et al., 2012). According to these studies, the role of yeasts seems crucial in the modulation of the human immune system, and it is evident that this mechanism is dependent on the strain-specific cell wall variability.

Adaptive traits of the innate immune system have been proven for invertebrates (Conrath et al., 2015; Gourbal et al., 2018; Kurtz, 2005). These insights are out of the scope of this review, but given the importance of the trained immunity in the fungi–host research field from a conceptual and applicative point of view, we highlighted some interesting examples. In particular, the activity of β-glucans in increasing the immune activity of shrimps toward pathogen infections has suggested their use in aquacultures (Amparyup et al., 2012; S. Roy et al., 2020). In insects, strains belonging to the species *S. cerevisiae* and *C. albicans* were proven to enhance the immune response against *C. albicans* reinfection in *Galleria mellonella* insect model (Bergin et al., 2006). *G. mellonella* also showed immune enhancement following the immune system exposure with the cell wall of *Aspergillus fumigatus* (Fallon et al., 2011; Mowlds et al., 2008, 2010; Mowlds & Kavanagh, 2008) and *C. glabrata* (X.-W. Huang et al., 2020). Similarly, in social wasp *Polistes dominula* an immune enhancing mechanism against generic pathogen *Escherichia coli* following exposure with *S. cerevisiae* was highlighted (Meriggi et al., 2019). Fungal-mediated immune priming was also depicted in *Drosophila melanogaster* following treatment with the entomopathogenic fungus *Beauveria bassiana* (Pham et al., 2007). These immune mechanisms are considered a crucial evolutionary strategy for insect survival (Cooper & Eleftherianos, 2017), and highlights the evolutionary convergence in the mechanisms of tolerance and defense toward the resident fungal community or pathogens. Moreover, these studies provide evidence that helps in understanding the molecular mechanisms underlying adaptive traits of innate immunity.

4 | CONCLUSION

Fungi have accompanied human evolution, spreading into the environment and becoming part of our diet since the advent of the Neolithic Revolution and the production of fermented beverages.

Within the fungal kingdom, *Ascomycota* phylum contains the larger number of species described to interact with the human host, either as beneficial or pathogenic microorganisms. *Ascomycota* yeasts, such as *Saccharomyces* species, can act as probiotics promoting our health or they can be pathogens capable of threatening humans and animals. At the same time, *Candida* species are known to colonize multiple body sites, both as commensals and pathogens. Together with these two predominant genera, many other fungal species create a close relationship with the host, influencing its physiology, functions, and overall health. Cell wall components play a central role in the modulation of host immune response ranging from innate to cell-mediated and humoral adaptive forms. The recent discovery of immune enhancement mediated by fungal trained immunity reveals a new concept in immunity, helping us to understand the beneficial role of yeasts, but also showing that yeasts can exploit the immune system of the host to fight other yeasts or bacteria. The findings discussed in this review show the importance of investigating the interactions between the yeast component of the microbiota and their host in a holistic way. Only using evolution as a magnifying lens together with modern systems level analyses we will be able to understand their transition from passengers to colonizers and invaders, and unravel the subtle networks discriminating the role of the mycobiota in health from disease.

AUTHOR CONTRIBUTIONS

Stefano Nenciarini: Conceptualization (supporting); investigation (equal); visualization (equal); writing – original draft (lead); writing – review and editing (equal). **Sonia Renzi:** Investigation (equal); visualization (equal); writing – original draft (lead); writing – review and editing (equal). **Monica Di Paola:** Visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Niccolò Meriggi:** Visualization (supporting); writing – original draft (equal); writing – review and editing (equal). **Duccio Cavalieri:** Conceptualization (lead); funding acquisition (lead); project administration (lead); supervision (lead); writing – review and editing (equal).

FUNDING INFORMATION

This review was funded by the University of Florence, by the Joint Programming Initiative, Eranet Cofund, a Healthy Diet for a Healthy Life (JPI-HDHL), TRANSMIC project (grant number 529051018), Regione Toscana-Bando Salute 2018 RISKCROHNBIOM project (grant number G84I18000160002). This work was funded by the Italian Ministry of Agriculture, Food, and Forestry Policies (MiPAAF), within the trans-national project INTIMIC–Knowledge Platform on food, diet, intestinal microbiomics, and human health of the Joint Programming Initiative Healthy Diet for a Healthy Life (JPI-HDHL), Expression of Interests no. 795 (MICROFLUX Project), 868 and 895 (MiPAAF DM 36954/7303/18) and by the Joint Programming Initiative a Healthy Diet for a Healthy Life-Intestinal Microbiomics (JPI HDHL-INTIMIC) Call for Joint Transnational Research Proposals on "Interrelation of the Intestinal Microbiome, Diet and Health" (reference number JTC-2017-7).

CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Nenciarini, S., Renzi, S., di Paola, M., Meriggi, N., & Cavalieri, D. (2024). The yeast–human coevolution: Fungal transition from passengers, colonizers, and invaders. *WIREs Mechanisms of Disease*, *16*(3), e1639. https://doi.org/10.1002/wsbm.1639