Immunosurveillance of *Candida albicans* commensalism by the adaptive immune system

Marc Swidergall\(^1\,2,3\) and Salomé LeibundGut-Landmann\(^4,5,6,7\)

© The Author(s) 2022

The fungal microbiota (mycobiota) is an integral part of the microbial community colonizing the body surfaces and is involved in many key aspects of human physiology, while an imbalance of the fungal communities, termed fungal dysbiosis, has been described in pathologies ranging from infections to inflammatory bowel disease. Commensal organisms, such as the fungus *Candida albicans*, induce antigen-specific immune responses that maintain immune homeostasis. Adaptive immune mechanisms are vital in this process, while deficiencies in adaptive immunity are linked to fungal infections. We start to understand the mechanisms by which a shift in mycobiota composition, in particular in *C. albicans* abundance, is linked to immunopathological conditions. This review discusses the mechanisms that ensure continuous immunosurveillance of *C. albicans* during mucosal colonization, how these protective adaptive immune responses can also promote immunopathology, and highlight therapeutic advances against *C. albicans*-associated disease.

*Mucosal Immunology* (2022) 15:829–836; https://doi.org/10.1038/s41385-022-00536-5

INTRODUCTION

Fungi are an integral part of the human microbiota interacting with the immune system and affecting human physiology. The human mycobiota is composed of 390 different fungal species belonging to the phyla *Ascomycota*, *Basidiomycota*, and *Zygomycota*

\(^1\), which are required for microbial community structure, metabolic function, and immune priming. \(^2\)-\(^4\). *Candida* species such as *Candida albicans* are commonly found on the oral, gastrointestinal, and vaginal mucosae. Besides its host-beneficial effects protecting the host from various microbial insults, *C. albicans* can itself become pathogenic and cause diverse pathologies in immunocompetent and immunocompromised individuals. *Candida*-mediated disorders range from mild superficial infections such as neonatal thrush to extensive and/or recurrent infections of the esophageal or vaginal tract that can cause significant morbidity. \(^5\) Translocation of *Candida* across epithelia and fungal dissemination through the bloodstream can finally result in life-threatening systemic manifestations, which are responsible for several hundred thousand annual deaths worldwide. \(^6\) In addition, *C. albicans* is also associated with inflammatory not primarily infectious diseases, such inflammatory bowel disease (IBD). \(^7\) Given the continuous presence of *C. albicans* in barrier tissues and their significant pathogenic potential, tight control of the fungus at the host interface is a prerequisite of homeostasis. The adaptive immune system plays a key role in providing long-lasting defence against uncontrolled fungal growth, acquisition of virulence traits, and invasion of normally sterile tissues.

Evidence for a protective role of T cells against *C. albicans* is provided by individuals displaying an enhanced susceptibility for mucocutaneous candidiasis due to acquired or inherited defects in the frequency, activation, or function of CD4\(^+\) T cells, especially those producing IL-17. \(^8\)-\(^9\) Although historically, the evidence for antibodies contributing to fungal control was sparse, recent studies highlight the relevance of antibody-mediated immunity in maintaining *C. albicans* commensalism. \(^10\)-\(^12\) Key hallmarks of cellular and humoral adaptive immunity are the antigen-specificity, which accounts for the directionality of the response, the requirement for lymphocytes to undergo tightly regulated differentiation and polarization processes, which generate highly specialized and qualitatively distinct responses, and the capacity to form long-lasting memory.

Here, we review the current understanding of T- and B-cell mediated antifungal defence in barrier tissues, discuss how these normally protective immune mechanisms can also promote immunopathology under certain conditions, and highlight outstanding challenges that still impede harnessing our knowledge for preventative & therapeutic advances against *Candida*-associated (infectious and non-infectious) disorders.

### T CELL-MEDIATED IMMUNITY AGAINST *C. ALBICANS*

*C. albicans*-responsive CD4\(^+\) T cells are primed in all healthy individuals as a consequence of their constant exposure to the fungus. \(^13\)-\(^14\) They are characterized predominantly by a Th17 profile producing IL-17A, IL-17F and IL-22, with a minor fraction belonging to the Th1 or Th2 subsets. \(^15\) While most studies assessing human antifungal T cells focused on circulating T cells due to their easy accessibility in the blood, *C. albicans*-specific Th17 cells have also been evidenced in the healthy skin. \(^16\) Similarly, in experimental models of oropharyngeal candidiasis...
innate-like T cells and ILCs. Different dendritic cell subsets including IL-23, IL-6 and IL-1 contribute also to the activation of the fungus during commensalism in colonized tissue remains to be determined. Rapid decline of the antifungal T cell population following antimycotic-mediated removal of the fungus indicates that maintenance of the homeostatic Th17 response depends on the continuous presence of the fungus. This is reminiscent of the situation of other commensal- and virus-specific tissue-resident CD4+ T cells responses. The dependence on fungal persistence may reflect the requirement for continuous antigen recognition by commensal-specific Th17 cells, as shown to be the case for homeostatic Th1 cells in the skin, which depend on keratinocyte-intrinsic MHC-II. Alternatively, fungal persistence might induce cytokine signals for homeostatic T cell survival, proliferation and/or renewal or modulate the microenvironment in another way to favour T cell persistence. The observed dependence of the C. albicans-specific T cell response on the continuous presence of the fungus contradicts the paradigm of immunological memory. Therefore, clarification of the relationship between homeostatic T cells providing immunosurveillance of commensals and memory T cells that protect against recurring infections awaits further investigations. Taken together, long-lived Th17 cells residing in the colonized tissue are the most notable ones of the diverse lymphoid responses that in C. albicans pathogenicity. The tonic signal controlling long-term maintenance of antifungal T cells during commensalism in colonized tissue remains to be determined. Rapid decline of the antifungal T cell population following antimycotic-mediated removal of the fungus indicates that maintenance of the homeostatic Th17 response depends on the continuous presence of the fungus. This is reminiscent of the situation of other commensal- and virus-specific tissue-resident CD4+ T cells responses. The dependence on fungal persistence may reflect the requirement for continuous antigen recognition by commensal-specific Th17 cells, as shown to be the case for homeostatic Th1 cells in the skin, which depend on keratinocyte-intrinsic MHC-II. Alternatively, fungal persistence might induce cytokine signals for homeostatic T cell survival, proliferation and/or renewal or modulate the microenvironment in another way to favour T cell persistence. The observed dependence of the C. albicans-specific T cell response on the continuous presence of the fungus contradicts the paradigm of immunological memory. Therefore, clarification of the relationship between homeostatic T cells providing immunosurveillance of commensals and memory T cells that protect against recurring infections awaits further investigations. Taken together, long-lived Th17 cells residing in the colonized tissue are the most notable ones of the diverse lymphoid responses that in C. albicans pathogenicity.
overgrowth and tissue invasion by strengthening the antimicrobial effector functions and the barrier integrity of the epithelium. Reinforcement of the barrier function and protection from intestinal injury in the gut was attributed to IL-22, which is produced by antifungal Th17 cells in addition to IL-17A and IL-17F. Of note, the T cell response mounted in response to fungal colonization enhances resistance not only against the mycobacteria itself but also against bacterial infections as shown in experimental models with *C. difficile* and *C. rodentium*.

While an impairment of the IL-17/IL-22 pathway predisposes individuals to mucocutaneous candidiasis, the same fungal infection also manifests in individuals with an intact antifungal Th17 response but a dysregulated balance between type 17 and type 1 immunity. As such, APECED patients suffering from chronic mucocutaneous candidiasis (CMC) exhibit exacerbated type 1 responses while type 17 immune responses are intact. Aire-deficient mice recapitulating the situation in APECED patients revealed that IFN-γ-driven interferonopathy drives pronounced epithelial barrier defects, which underlie the mucosal fungal susceptibility. Barrier-protective effects of type 17 immunity can thus be overridden by aberrant IFN-γ/STAT1 responses that promote epithelial cell death and barrier disruption.

Beyond the local host-protective effects, *C. albicans*-induced Th17 immunity has also been reported to mediate systemic antimicrobial effects, including heterologous protection from systemic *S. aureus*. Mechanistically, it was proposed that Th17 primed locally in the gut promote systemic neutrophil activation to enhance protection against an intravenous challenge. Moreover, the mycobacteria can impact physiological processes beyond host protection. As such, fungal gut colonization was recently proposed to promote social behaviour in mice. The neuromodulatory role of mucosa-associated fungi occurs in an IL-17-dependent manner with neuronal cells acting as direct targets of IL-17. This expands the previously noted effects of IL-17 on social behaviour and provides a mechanistic basis for the reported associations of fungal dysbiosis and neuropsychiatric conditions in humans.

During homeostasis, *C. albicans*-specific Th17 cells are not associated with inflammatory processes despite their continuous engagement by the commensal fungus and the proinflammatory potential of IL-17. This is reminiscent of homeostatic T cells directed against commensal bacteria in the gut, which display a metabolic profile characteristic of resting memory cells. Whether immunoregulatory processes contribute to stable homeostasis by actively preventing plasticity of *C. albicans*-specific homeostatic Th17 cells towards pathogenicity (see below) remains currently unclear with no evidence for a contribution of regulatory T cells or of IFN-γ.

Moreover, the antifungal effects of Th17 cells during fungal commensalism are not accompanied by an accumulation of neutrophils in the colonized tissue, which would be incompatible with homeostasis, even though neutrophil-recruiting chemokines are stimulated by IL-17 under some conditions. Examples of mucocutaneous *C. albicans* infections characterized by a strong neutrophil response in the infected tissue are those from experimental cutaneous and oropharyngeal infections with highly virulent strains of *C. albicans*, where the inflammatory response is an acute and direct reaction to fungal virulence factors and release of keratinocyte-derived alarmins such as IL-10, and is largely independently of the IL-17 pathway. In conclusion, the homeostatic role of IL-17 is non-inflammatory and expands beyond microbial control, and it may be mediated by mechanisms beyond strengthening antimicrobial barrier functions of the epithelium (Fig. 1A).

**Antibody-Mediated Immunity Against *C. Albicans***

Antibodies play a vital role in homeostasis and protective immunity at mucosal sites, as well as during systemic infections, and can be divided into five isotypes, which operate in distinct places and have distinct effector functions. Antibody effector functions have classically been studied in the context of pathogenic infections. However, it is apparent that luminal and serum antibodies bind members of the microbiota.

The fungal cell wall contains various pattern-associated molecular patterns (PAMPs), such as β-glucans, for innate immune recognition. However, the *C. albicans* cell wall and secretory proteins are also a significant source of antigens. During the course of an immune response, depending on the nature of the eliciting antigen and its entry mode, class-switch recombination (CSR) replaces immunoglobulin constant regions for the isotype that can best protect against commensal or pathogenic microorganism. As a result, mature B cells express antibodies of the IgA, IgG, or IgE classes that differ in effector functions without altering the specificity for the immunizing antigen. Intestinal *C. albicans* colonization induces distal CSR and B cell expansion in germinal centers (GC) to induce high-affinity IgM. CSR and GC-B cell expansion is controlled by CARD9 and CX3CR1, mononuclear phagocytes (MNP), and antifungal IgG responses are reduced in patients with polymorphisms in the coding region of the CX3CR1 or CARD9 genes, in whom CD has been described. Furthermore, CARD9-deficient patients manifest fungal-specific infection susceptibility, predominantly in the central nervous system.

A significant portion of *C. albicans* is recognized by systemic antifungal IgG antibodies in humans and mice, where IgG3 binds the largest fraction of intestinal fungi. IgG3 Abs are potent mediators of effector functions, including enhanced Ab-mediated cellular cytotoxicity, opsonophagocytosis, complement activation, and neutralization, compared with other IgG subclasses. Accordingly, mucosal fungal colonization induces distal humoral immunity and systemic protection against invasive candidiasis.

Cross-reactive antibody responses provide protective immunity to related pathogens or antigenic variants in natural epidemiology. In this line, intestinal-induced anti-*C. albicans* IgG protects against systemic infection with the emerging drug-resistant fungus *C. auris*. However, IgG isotypes generated by intestinal *C. albicans* colonization are not cross-reactive with environmental, food-derived, or skin-resident fungi such as *Saccharomyces*, *Aspergillus*, and *Malassezia* spp.

IgA is the dominant isotype at mucosal barriers, and predominantly induced in response to colonization with commensal organism to maintain homeostasis. Within the mucosa, commensal-specific microorganisms are coated by low-affinity and antifungal-specific secretory IgA (SIgA). Furthermore, IgA serves as the first line of defense in protecting the epithelium, from toxins or potential pathogenic microorganism overgrowth. While immune exclusion is a dominant IgA effector mechanism, IgA is able to enchain pathogens, thereby preventing organism separation after replication resulting in clumping. Accordingly, mucosal *C. albicans* colonization induces IgA to reduce fungal-associated virulence attributes. IgA binding to *C. albicans* prevents adhesion, invasion, and damage of epithelial cells, resulting in reduced inflammation. In particular, IgA binds to hyphae-associated virulence factors, such as *C. albicans* adhesins or the toxin candidalysin. Consequently, IgA binding controls commensal homeostasis by eliminating *C. albicans*-associated virulence traits, while the absence of IgA results in mucosal dysbiosis. *C. albicans* overgrowth, and pathology. Associated pathology is observed in patients with CD, in whom reduced virulence factor targeting SIgA have been described and in NDV3 vaccinated mice, which generate IgA against the adhesion Als3 and have reduced pathology during DSS-induced colitis. Together, by modulating the *C. albicans* virulence IgA-dependent immunity favours fungal commensalism and homeostasis at mucosal barriers.

Most antibody-secreting cells (ASCs) in mucosal tissues produce IgA. Oral mucosal *C. albicans* colonization increases CD19+ CD138+ B cell, plasmablast, and plasma cell enrichment in the
mucosa\textsuperscript{11}, while intestinal colonization increases the Ig\textsuperscript{A}\textsuperscript{+} frequency and strong IgA CSR in the PP B cell compartment associated with high-affinity antibody responses\textsuperscript{50}. These IgA responses are mediated through innate immune interaction with intestinal CD11c\textsuperscript{+}CD11b\textsuperscript{+}CD103\textsuperscript{+} dendritic cells and CX3CR1\textsuperscript{+}MNP\textsuperscript{+}. Trafficking of IgA ASCs is regulated by a combination of chemokine receptors as well as integrins\textsuperscript{46}. Recent evidence points at a role for gut-educated IgA ASCs in modulating antifungal immune responses outside of mucosal tissues. During homeostasis, meninges, the membranes surrounding the brain and spinal cord, contain gut-derived and commensal-specific IgA ASCs\textsuperscript{77}. Mice lacking IgA or with a selective loss of meningeal IgA plasma cells exhibit reduced protection against C. albicans and is associated with increased fungal invasion of the brain\textsuperscript{14}.

StgA can cross-react with a diverse fraction of the microbiota by canonical Fab-dependent and non-canonical carbohydrate-dependent binding\textsuperscript{75}. Oral mucosal colonization with C. albicans increases total levels of cross-specific IgAs against the common oral commensal Streptococcus oralis\textsuperscript{11} suggesting that fungal colonization and cross-reactive IgA responses shape the microbial community.

B cells have diverse antibody-independent functions, such as production of regulatory and pro-inflammatory cytokines, as well as antigen presentation and T cell stimulation\textsuperscript{96}. Human B cells can present fungal antigens to T cells in an HLA-DR-restricted manner, provide critical costimulatory signals through CD80 and CD86, and induce Th17 cell differentiation through an IL-6-dependent mechanism\textsuperscript{77}, while secretion of IL-6 depends on hyphal stimulation and is mediated by MyD88\textsuperscript{78}.

Collectively, mucosal C. albicans colonization induces a variety of antibody responses, which not only restrict fungal overgrowth, but also limit virulence, locally and systematically (Fig. 1A).

**EFFECTS OF THE ADAPTIVE ANTIFUNGAL IMMUNITY ON THE INTRASPECIES DIVERSITY OF C. ALBICANS**

C. albicans displays high intraspecies diversity, notably variations in the distribution of heterozygous polymorphisms along the genome\textsuperscript{79–81}. Genetically distinct isolates differ in their phenotype such as the degree of filamentation, expression of virulence factors, the induction of epithelial cell damage or the degree of inflammation-induced at the host interface. These phenotypic variations translate in differential outcomes of the interaction with the host as evidenced when probing genetically distinct isolates in model hosts which exclude any inter-individual differences on the host side prior to infection\textsuperscript{20,79,82–84}. From studying large sets of isolates it became clear that the high-virulent strain SC5314, which is broadly used in in vitro and in vivo experimental studies, is a poor colonizer of mucosal surfaces in immunocompetent hosts\textsuperscript{20,85} and thereby represents rather an outlier than the norm within the species of C. albicans\textsuperscript{26}. Despite striking differences between high- and low-virulent isolates in their efficiency to colonize mucosal surfaces, the adaptive immune response mounted in response to oral colonization is surprisingly comparable with strong T cell and antibody responses induced against widely differing isolates\textsuperscript{20,80,82}. This is consistent with the observation that all human individuals mount a C. albicans-specific T cell and antibody response, irrespective of the isolate that they are colonized with\textsuperscript{10,12–14}. This suggests that C. albicans virulence and immunogenicity are largely uncoupled for T cell priming in the oral mucosa and that antigens, as well as PRR ligands mediating dendritic cell activation for efficient lymphocyte priming, are more strongly conserved between isolates than the expression of virulence factors. PAMP exposure by C. albicans seems to depend on the body site of isolation\textsuperscript{86}. Moreover, because C. albicans actively masks PAMPs in response to its environment to reduce immune recognition\textsuperscript{87}, niche-specific colonization and consequently PAMP exposure may influence immune activation and thereby favour commensalism.

Adaptive immunity can modulate the pathogenicity of C. albicans\textsuperscript{10,12}. Thus, variations in the activity of antibody and/or T cell effector functions over time may generate a spectrum of phenotypes within an individual. If different phenotypes become epigenetically stabilized through DNA methylation\textsuperscript{88} or genetically fixed over time through (micro)evolutionary processes, this might contribute to the generation of genetic diversity. Indeed, C. albicans also undergoes genomic rearrangement during oral infection of mice\textsuperscript{89}. Growth in the oral mucosa of mice selects for trisomy of chromosome 6, resulting in a commensal-like phenotype\textsuperscript{90}. Importantly, C. albicans within-host diversity was also observed in humans and appears common in the context of commensalism as demonstrated by recent genome sequencing of isolates collected from single healthy individuals, which showed that they differed by numerous single nucleotide polymorphisms and short-range loss-of-heterozygosity (LOH)\textsuperscript{91}. C. albicans genomic and epigenetic variations can facilitate adaptation to environmental changes and improve the persistence of the fungus in various host niches\textsuperscript{92}. When considering inter-individual variations in the host adaptive immune activity, including those arising from to the increasing population of immunocompromised individuals, lineage diversification resulting from the close contact of C. albicans with the human host is an important driver of the genetic diversity observed within the species of C. albicans\textsuperscript{92–94}. Therefore, mutual adaptations of C. albicans and its mammalian host shape the outcome of their interaction both, at an individual's level as well as at a population scale.
as a decisive factor for enhanced inflammation in IBD patients. In light of the harmful rather than protective effects of IL-17 blockade in inflammatory bowel disease (IBD) patients, the role of C. albicans-specific Th17 cells in CD pathogenesis remains controversial. Whether C. albicans-specific T cells acquire pathogenicity in the context of colitis and which factors would drive such functional plasticity remains unclear. Serum amyloid A (SAA) is one factor proposed to promote the development of colitogenic Th17 cells in the gut in a C. albicans-independent context. Alternatively, C. albicans-specific Th17 may exert host-protective effects in the inflamed gut, presumably via strengthening barrier repair functions or by targeting translocated microbes. This notion is supported by the observation that C. albicans can enhance protection from colitis in experimental models, although T cell-dependence of this effect was not elaborated in all cases.

C. albicans-specific Th17 cells are not restricted to colonized epithelia but can also be found systemically and in distant organs such as the lung, where C. albicans is not a common resident. Th17 cells are strongly expanded in the inflamed lung of chronic obstructive pulmonary disease (COPD) and asthma patients, which are frequently sensitized to Aspergillus. In fact, Th17 cells responding to A. fumigatus also responded to C. albicans. Thereby, normally protective intestinal Th17 responses mounted against C. albicans are directly linked to lung pathologies caused by airborne fungi, albeit without signs of plasticity towards Th2 as observed in the skin. While bystander activation via T cell receptor-independent mechanisms cannot be excluded for the dual responsiveness of these cells, cross-reactivity has emerged as a common mechanism for the modulation of immune responses by the microbiota. Of note, the majority of Th17 cells responsive against widely diverse fungal species are cross-reactive to C. albicans suggesting broad modulation of human anti-fungal Th17 responses by a single fungal species. Antigen-specificity is a key hallmark of adaptive immunity. Only a few fungal antigens have been identified so far. Knowing the antigenic epitopes recognized by antifungal T cells is an important basis for understanding the mechanism that underlies the cross-reactivity of C. albicans-specific T cells. Towards that goal, several protein targets of cross-reactive T cells have been identified in A. fumigatus proteins displaying sequence similarity with their homologues in C. albicans. Identification of C. albicans epitopes further offers the possibility to track fungal-specific T cells in the endogenous repertoire in an antigen-specific manner by means of MHC tetramers, providing a high-resolution approach to dissect immune responses directed against the mycobacteria in health and disease, and it may reveal new targets for diagnostics and therapy.

**Antibody-mediated immunopathologies**

Antibodies against fungal cell wall components and embedded proteins have been associated with various pathological conditions. Anti-Saccharomyces cerevisiae antibodies (ASCA), which target cell-wall components in Saccharomyces and Candida species were found elevated in the serum (IgG) and intestinal lumen (IgA) of CD patients. High ASCA levels are a consequence of intestinal injury suggesting that ASCA is not an epiphenomenon but is probably due to a cross-reactivity with antigens involved in the immunopathology of CD. Mannans from other yeasts, such as C. albicans, can cross-react with ASCA suggesting that other yeast may induce ASCA-associated diseases. In fact, in a mouse model of dextran sulfate sodium (DSS)-induced colitis C. albicans colonization generates ASCA and promotes inflammation. In this context, systemic ASCA develops consistently in patients with CD where fungal dysbiosis and outgrowth of Candida species have been described. Furthermore, an increase in Candida abundance and serum ASCA generation was shown in patients with alcohol-associated liver disease. ASCA levels correlated with disease severity and increased mortality, and were reversed upon 2 weeks of alcohol abstinence. Similarly, anti-C. albicans antibodies were also elevated in non-alcoholic fatty liver disease patients and correlated with the degree of fibrosis. Antifungal therapy prevented ethanol-induced liver disease in mice, although it remained open whether this effect was mediated in an antibody-dependent manner and whether fungal dysbiosis and C. albicans overgrowth increased inflammatory responses independently of ASCA to promote pathological conditions.

In autoimmune diseases, autoantibodies (auto-Abs) often develop before any clinical symptoms can be detected. While fungal dysbiosis has not been associated with the generation of auto-Abs, antibodies against cytokines and chemokines involved in mucosal anti-fungal immunity were proposed to predispose for C. albicans outgrowth and infection. High antibodies titers against IL-17A, IL-17F, and IL-22 can be found in patients with CMC and autoimmune polyendocrine syndrome type III. However, some patients with persistent IL-17 auto-Abs lack CMC, and some patients with CMC lack auto-Abs suggesting the existence of CMC subtypes across a spectrum of impaired type 17 immunity, whereby in patients with an intact IL-17 pathway CMC was shown to develop as a consequence of immunopathology caused by excessive type 1 inflammation.

**VACCINES AGAINST C. ALBICANS**

Vaccines are among the most successful public health interventions resting on the principle of immune memory, whereby a secondary challenge induces an enhanced immune response against a previously encountered pathogen. The fact that C. albicans has coevolved with humans for at least 2,000 years, that this fungus is a lifelong inhabitant of mucosal surfaces, and every colonized individual harbour a memory response directed against C. albicans, presents a number of conceptual and technical challenges in the development of an anti-C. albicans vaccine. Furthermore, rather than acquisition, C. albicans infections result from translocation or fungal outgrowth, implying that anti-C. albicans vaccines should target specific virulence factors to diminish pathogenic attributes. The use of the N-terminal region of C. albicans agglutinin like sequence 3 protein (Als3) is the most promising and advanced vaccination strategy yet tested. This vaccine, referred to as NDV-3, induces T cell, IgG, and IgA responses in mice and humans. NDV-3 vaccinated mice are protected against systemic and mucosal C. albicans infection, while inducing cross-reactive protective responses against C. auris and Staphylococcus aureus in mice. Furthermore, NDV-3 vaccination prevents C. albicans-associated damage in mice with colitis by inducing fungal adhesin-specific IgA responses. Importantly, NDV-3 has been shown to be safe and efficacious in a clinical trial against recurrent vulvovaginal candidiasis. A different study uses the recombinant C. albicans secreted aspartyl proteinase 2 (Sap2) protein. Sap2 plays an important role in fungal pathogenesis by degrading host proteins at mucosal sites and inactivate complement components. Vaccination with Sap2 results in the generation of antigen specific protective antibodies, which cross-react with different members of the Sap family. These strategies demonstrate that vaccination against C. albicans virulence factors not only protects against this fungus itself, thus, preventing pathology at different body sites, but also provide protection against other fungi, and even bacteria. As a result, research into the production of universal fungal vaccines has gained traction in the scientific community, which may not only aid in the discovery of novel fungal vaccine candidates from unexpected and distant species but may also aid in repurposing of some of the effective vaccines used against other pathogens.
CONCLUDING STATEMENT
Informed by mouse studies and fuelled by new techniques, such as single cell RNA sequencing and spatial omics, human immunological research is advancing disease treatment while also generating insights into basic immunological concepts. This has led to exciting discoveries regarding the relevance and role of adaptive immunity in immuno-surveillance of Candida albicans, but also revealed pathological consequences that these responses can have in predisposed patients. However, most work to decipher human immune responses to C. albicans has been (understandably) limited to blood. Recently, Lioniaki and colleagues used oral mucosal biopsies of APECED patients with CMC to show that tissue-specific immunity is not always reflected by immune responses of circulating cells. Thus, studying tissues directly will aid our understanding of tissue-resident cell types (such as resident memory lymphocytes and tissue-specific stroma) and form of tissue-specific immune mechanisms driving or preventing pathologies. Accordingly, studying the diverse C. albicans-mediated pathologies requires usage of relevant mouse models. For instance, C. albicans infections and immune responses should be studied in colonized animals rather than naïve and acutely infected mice. In this line, commensal isolates, which are able to colonize fully immunocompetent animals, should be used to closely mimic scenes seen in patients.

REFERENCES
1. Gouba, N. & Drancourt, M. Digestive tract mycobiota: a source of infection. Med. et. maladies infectieuses 45, 9–16 (2015).
2. Underhill, D. M. & Pearlman, E. Immune interactions with pathogenic and commensal fungi: a two-way street. Immunity 43, 845–858 (2015).
3. Wheeler, M. L. et al. Immunological consequences of intestinal fungal dysbiosis. Cell Host Microbe 19, 865–873 (2016).
4. Iliev, I. D. & Leonardi, I. Fungal dysbiosis: immunity and interactions at mucosal surfaces. Nat. Rev. Immunol. 17, 635–646 (2017).
5. Revankar S. G., Sobel J. D. Mucosal Candidiasis. In: Calderone R. A., Clancy C. J. J. Allergy Clin. Immunol. 19, 865–873 (2016).
6. Gladioler, A., Wangler, N., Trautwein-Weidner, K. & LeibundGut-Landmann, S. Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection. J. Immunol. 190, 521–525 (2013).
7. Schmidt, F. A. et al. The intraspecies diversity of C. albicans triggers qualitatively and temporally distinct host responses that determine the balance between commensalism and pathogenicity. Mucosal Immunol. 10, 1335–1350 (2017).
8. Verma, A. H. et al. Oral epithelial cells orchestrate innate type 17 responses to Candida albicans through the virulence factor candidalysin. Sci. Immunol. 2, eaam8834 (2017).
9. Kesham, S. W. et al. Non-protective sensory fibers drive interleukin-23 production from CD301b+/− dermal dendritic cells and drive protective cutaneous immunity. Immunology 43, 515–526 (2015).
10. Morando, E. et al. Skin-resident murine dendritic cell subsets promote distinct and opposing antigen-specific Th helper cell responses. Immunology 35, 260–272 (2011).
11. Trautwein-Weidner, K. et al. Antigen-specific Th17 cells are primed by distinct and complementary dendritic cell subsets in oropharyngeal candidiasis. PLoS Pathog. 11, e1005164 (2015).
12. Korn, T., Bettelli, E., Oukka, M. & Kuchroo, V. K. IL-17 and Th17 cells. Annu. Rev. Immunol. 27, 485–517 (2009).
13. Ansald, E., Farley, T. K. & Belkaid, Y. Control of immunity by the microbiota. Annu. Rev. Immunol. 39, 449–479 (2021).
14. Ometto, S. et al. The intestine harbors functionally distinct homeostatic tissue-resident and inflammatory Th17 cells. Immunity 51, 77–89.e76 (2019).
15. Swaanakheka, N. et al. Th17 resident helper cells promote humoral responses in the lung. Sci. Immunol. 6, eabb6808 (2021).
16. Tamoutounour, S. et al. Kinorinocyt-intrinsic MHCI expression controls microbiota-induced Th1 cell responses. Proc. Natl. Acad. Sci. USA 116, 23643–23652 (2019).
17. Leonardi, I. et al. Mucosal fungi promote gut barrier function and social behavior via Type 17 immunity. Cell 175, 831–846.e124 (2019).
18. Markey, L. et al. Pre-colonization with the commensal fungus Candida albicans reduces murine susceptibility to Clostridium difficile infection. Gut Microbes 9, 497–509 (2018).
19. Break, T. J. et al. Ablanter type 1 immunity drives susceptibility to mucosal fungal infections. Science 371, eaay5731 (2021).
20. Zhao, T. Y. et al. Commensal Candida albicans Positively Calibrates Systemic Th17 Immunological Responses. Cell Host Microbe 25, 404–417.e406 (2019).
21. Tso, G. H. W. et al. Experimental evolution of a fungal pathogen into a gut symbiont. Science 362, 589–595 (2018).
22. Chen, C. et al. IL-17 is a neuromodulator of Caenorhabditis elegans sensory responses. Nature 542, 43–48 (2017).
23. Reed, M. D. et al. IL-17A promotes sociability in mouse models of neurodevelopmental disorders. Nature 577, 249–253 (2020).
24. Choi, G. B. et al. The maternal interleukin-17A pathway in mice promotes autism-like phenotypes in offspring. Science 351, 933–935 (2016).
25. Alves de Lima, K. et al. Meningeal gammadelta T cells regulate anxiety-like phenotypes in offspring. Mucosal Immunol. 10, 1259–1274 (2017).
26. Zou, R. et al. Dysbiosis of gut fungal microbiota in children with autism spectrum disorders. The microbiome-induced Th1 cell responses. Proc. Natl. Acad. Sci. USA 116, 23643–23652 (2019).
27. Leonardi, I. et al. Mucosal fungi promote gut barrier function and social behavior via Type 17 immunity. Cell 175, 831–846.e124 (2019).
28. Markey, L. et al. Pre-colonization with the commensal fungus Candida albicans reduces murine susceptibility to Clostridium difficile infection. Gut Microbes 9, 497–509 (2018).
29. Break, T. J. et al. Aberrant type 1 immunity drives susceptibility to mucosal fungal infections. Science 371, eaay5731 (2021).
30. Shao, T. Y. et al. Commensal Candida albicans Positively Calibrates Systemic Th17 Immunological Responses. Cell Host Microbe 25, 404–417.e406 (2019).
31. Tso, G. H. W. et al. Experimental evolution of a fungal pathogen into a gut symbiont. Science 362, 589–595 (2018).
32. Chen, C. et al. IL-17 is a neuromodulator of Caenorhabditis elegans sensory responses. Nature 542, 43–48 (2017).
33. Reed, M. D. et al. IL-17A promotes sociability in mouse models of neurodevelopmental disorders. Nature 577, 249–253 (2020).
34. Choi, G. B. et al. The maternal interleukin-17A pathway in mice promotes autism-like phenotypes in offspring. Science 351, 933–935 (2016).
35. Alves de Lima, K. et al. Meningeal gammadelta T cells regulate anxiety-like behavior via IL-17A signaling in neurons. Nat. Immunol. 21, 1421–1429 (2020).
36. Strati, F. et al. New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome 5, 24 (2017).
37. Zou, R. et al. Dysbiosis of gut fungal microbiota in children with autism spectrum disorders. J. Autism Dev. Disord. 51, 267–275 (2021).
38. Kirchner, F. R. et al. Persistence of Candida albicans in the oral mucosa induces a curbed inflammatory host response that is independent of immunosuppression. Front Immunol. 10, 330 (2019).
39. Huppler, A. R. et al. Rule of neutrophils in IL-17-dependent immunity to mucosal candidiasis. J. Immunol. 192, 1745–1752 (2014).
40. Trautwein-Weidner, K., Gladioler, A., Nur, S., Diethelm, P. & LeibundGut-Landmann, S. IL-17-mediated antifungal defense in the oral mucosa is independent of neutrophils. Mucosal Immunol. 8, 221–231 (2015).
41. Keppler, S. J., Goess, M. C. & Heinze, J. M. The wanderings of gut-derived IgA plasma cells: impact on systemic immune responses. Front Immunol. 12, 670290 (2021).
42. Dimitrov, J. D. & Lacaro-Desmazes, S. Noncanonical functions of antibodies. Trends Immunol. 41, 379–393 (2020).
43. Janeway, C. Immunobiology: The immune system in health and disease. (Garland Pub., New York, 2001).
44. Bollesensch, T. & Macpherson, A. J. Anti-commensal Ig—from enormous diversity to clear function. Mucosal Immunol. 13, 1–2 (2020).
45. Sterlin, D., Fadlallah, J., Slack, E. & Gorochov, G. The antibody/microbiota interface in health and disease. Mucosal Immunol. 13, 3–11 (2020).
46. Romani, L. Immunity to fungal infections. J. Allergy Clin. Immunol. 127, 285–298 (2011).
47. Lionakis, M. S. Gut mycobiota in immunity and in commensal fungi: a two-way street. Nat. Rev. Microbiol. 15:829 – 836 (2017).
117. Limon, J. J. et al. Malassezia is associated with Crohn’s disease and exacerbates colitis in mouse models. *Cell Host Microbe* **25**, 377–388.e376 (2019).

118. Issaie, E. et al. Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease. *Gut* **54**, 1232–1236 (2005).

119. Lewis, J. D. et al. Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric Crohn’s disease. *Cell Host Microbe* **18**, 489–500 (2015).

120. Hartmann, P. et al. Dynamic changes of the fungal microbiome in alcohol use disorder. *Front Physiol.* **12**, 699253 (2021).

121. Yang, A. M. et al. Intestinal fungi contribute to development of alcoholic liver disease. *Liver Transpl.* **23**, 1282–1289 (2017).

122. Hartmann, P. et al. Dynamic changes of the fungal microbiome in alcohol use disorder. *Front Physiol.* **12**, 699253 (2021).

123. Kullberg, B. J. & Arendrup, M. C. Invasive Candidiasis. *J. Clin. Endocrinol. Metab.* **98**, 3386–3405 (2013).

124. Schaller, M. et al. The secreted aspartyl proteinases Sap1 and Sap2 cause tissue damage in an in vitro model of vaginal candidiasis based on reconstituted human vaginal epithelium. *Infect. Immun.* **71**, 3227–3234 (2003).

125. Gropp, K. et al. The yeast Candida albicans evades human complement attack by secretion of aspartic proteases. *Mol. Immunol.* **47**, 465–475 (2009).

126. Svoboda, E. et al. Secreted aspartic protease 2 of Candida albicans inactivates factor H and the macrophage factor H-receptors C3d (CD11b/CD18) and C4d (CD11c/CD18). *Immunol. Lett.* **166**, 13–21 (2015).

127. Puel, A. et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis. *Cell Host Microbe* **18**, 92–111 (2021).

128. Browne, S. K. & Holland, S. M. Anti-cytokine autoantibodies explain some chronic mucocutaneous candidiasis. *Immunol. Cell Biol.* **88**, 614–615 (2010).

129. Orlova, E. M. et al. Expanding the phenotypic and genotypic landscape of the gut microbiome in pediatric Crohn’s disease. *Cell Host Microbe* **18**, 489–500 (2015).

130. Limon, J. J. et al. Malassezia is associated with Crohn’s disease. *J. Clin. Invest.* **127**, 1423–1430 (2017).

131. Doherty, M., Buchy, P., Standaert, B., Giaquinto, C. & Prado-Cohrs, D. Vaccine mission and microevolutions of Candida albicans isolates from the human vaginal epithelium. *Vaccine: lessons from the past and opportunities for the future*. In *Mucosal Immunology* (eds Flavell et al.) 1–12 (Springer Nature, 2022).

132. Shukla, M., Chandley, P. & Rohatgi, S. The Role of B-cells and antibodies against Candida vaccine antigens in invasive candidiasis. *Vaccines* **9**, 1159 (2021).

133. De Bernardis, F. et al. Protective role of antimannan and anti-aspartyl proteinase antibodies in an experimental model of Candida albicans vaginitis in rats. *Infect. Immun.* **65**, 3399–3405 (1997).

134. Schmidt, C. S. et al. NDV-3, a recombinant alum-adjuvanted vaccine for Candida albicans infection in mice. *PLoS Pathog.* **3**, e1000703 (2009).

135. Svoboda, E. et al. Secreted aspartic protease 2 of Candida albicans inactivates factor H and the macrophage factor H-receptors C3d (CD11b/CD18) and C4d (CD11c/CD18). *Immunol. Lett.* **166**, 13–21 (2015).

136. Lin, L. et al. Th1-Th17 cells mediate protective adaptive immunity against Staphylococcus aureus infection in mice. *PLoS Pathog.* **15**, e1007460 (2019).

137. Gropp, K. et al. The yeast Candida albicans evades human complement attack by secretion of aspartic proteases. *Mol. Immunol.* **47**, 465–475 (2009).

138. Alqarihi, A., Singh, S., Edwards, J. E. Jr., Ibrahim, A. S. & Uppuluri, P. NDV-3A, a recombinant alum-adjuvanted vaccine for Candida albicans infection in mice. *PLoS Pathog.* **3**, e1000703 (2009).

139. Schaller, M. et al. The secreted aspartyl proteinases Sap1 and Sap2 cause tissue damage in an in vitro model of vaginal candidiasis based on reconstituted human vaginal epithelium. *Infect. Immun.* **71**, 3227–3234 (2003).

140. Gropp, K. et al. The yeast Candida albicans evades human complement attack by secretion of aspartic proteases. *Mol. Immunol.* **47**, 465–475 (2009).

141. Svoboda, E. et al. Secreted aspartic protease 2 of Candida albicans inactivates factor H and the macrophage factor H-receptors C3d (CD11b/CD18) and C4d (CD11c/CD18). *Immunol. Lett.* **166**, 13–21 (2015).

142. De Bernardis, F. et al. Protective role of antimannan and anti-aspartyl proteinase antibodies in an experimental model of Candida albicans vaginitis in rats. *Infect. Immun.* **65**, 3399–3405 (1997).

143. Shukla, M., Chandley, P. & Rohatgi, S. The Role of B-cells and antibodies against Candida vaccine antigens in invasive candidiasis. *Vaccines* **9**, 1159 (2021).

144. Schaller, M. et al. The secreted aspartyl proteinases Sap1 and Sap2 cause tissue damage in an in vitro model of vaginal candidiasis based on reconstituted human vaginal epithelium. *Infect. Immun.* **71**, 3227–3234 (2003).