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

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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.

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, gastro-intestinal, 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

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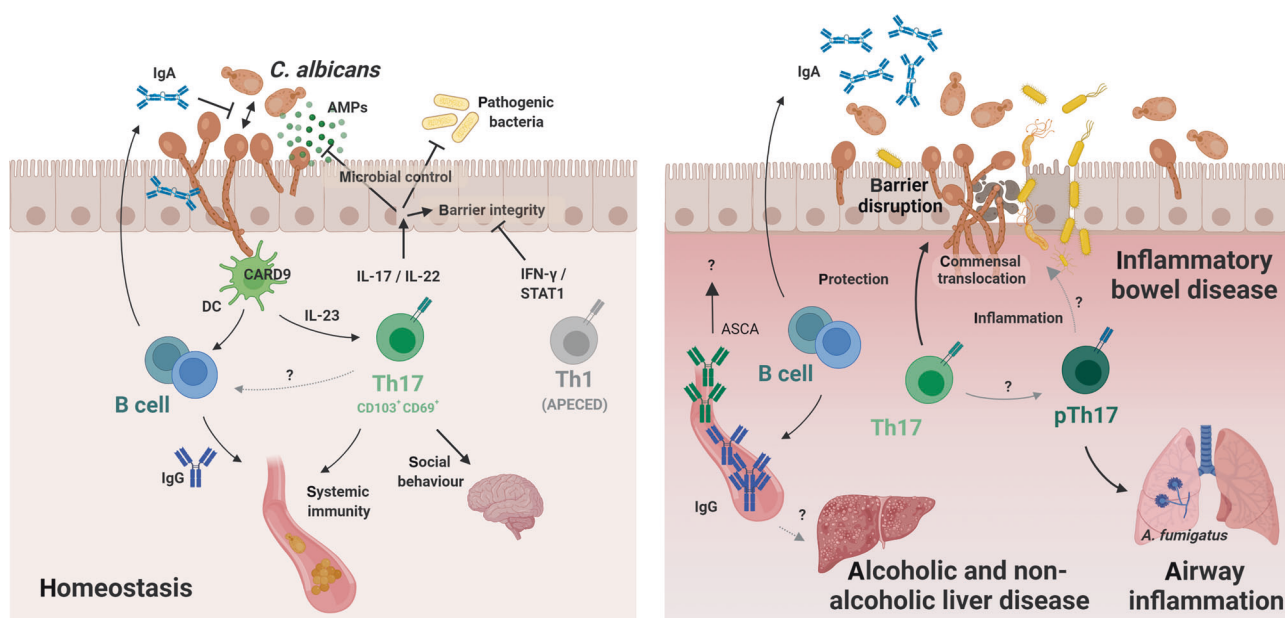
Fig. 1 Adaptive immunity against *C. albicans* in health and disease. (Left). Homeostatic immunity against *C. albicans* is maintained by cellular and humoral adaptive immunity. *C. albicans* drives fungus-specific and tissue-resident Th17 cells. IL-17 and IL-22 contribute to fungal control by promoting antimicrobial and barrier functions of the epithelium, the latter of which is counteracted by overt IFN-γ/STAT1-signalling. Antifungal Th17 immunity can also promote barrier defence against heterologous infections, both locally and systemically, and modulate social behaviour. Mucosal IgA targets fungal virulence determinants to repress *C. albicans* pathogenicity. *C. albicans*-specific IgG contributes to systemic antifungal immunity. **(Right).** Enhanced *C. albicans*-specific T cell and antibody responses have been observed in patients with gut barrier defects as in IBD. Whether IgA and Th17 cells act in a host-protective manner or whether antifungal T cells adopt features of pathogenic Th17 cells in the inflamed gut remains unclear. During airway inflammation, *C. albicans*-specific pathogenic Th17 cross-react with *A. fumigatus*. Enhanced *C. albicans*-reactive IgG antibodies have been associated with alcoholic and non-alcoholic liver disease, albeit their role in disease pathogenesis remains to be determined. See text for more details. The figure was generated with BioRender.com.

(OPC) and epicutaneous candidiasis, *C. albicans*-specific T cells with a selective Th17 phenotype are detected in the colonized epithelial tissue within a week of infection[17,18]. In addition to Th17 cells, innate-like T cells and TCR-negative innate lymphoid cells (ILCs) also contribute to the overall IL-17 production in mice where these IL-17 producers rapidly accumulate in response to the primary exposure of the murine host with the fungus, especially in response to virulent strains of *C. albicans*, which only transiently colonize mice[19–22]. The diverse cellular subsets appear to play redundant roles[19], with γδ T cells being particularly prominent/important during cutaneous experimental candidiasis[22].

The signals driving polarization of *C. albicans*-specific Th17 cells including IL-23, IL-6 and IL-1 contribute also to the activation of innate-like T cells and ILCs[19,21,23,24]. Different dendritic cell subsets have been implicated at the interface between the fungus and IL-17-production in the initiation of the response depending on the IL-17-producing cellular subset and the tissue compartment (skin vs. mucosa)[23,25,26]. In addition, neurons (in the skin) can sense the fungus and link fungal recognition to the induction of IL-23 by dermal DCs[22]. Moreover, the cellular damage caused by the fungal peptide toxin candidalysin, which is secreted by high virulent strain of *C. albicans*, contributes to IL-1 release for rapid IL-17 induction by innate-like T cells[21].

The continuous presence of *C. albicans* during commensalism requires a long-lived response for maintenance of homeostasis over time. As such, *C. albicans*-reactive Th17 in humans exhibit a memory phenotype[13]. Within barrier tissues, they express markers characteristic of tissue-resident memory T (T$_{RM}$) cells[16]. This has also been reproduced in experimental mice that have been persistently colonized with *C. albicans* to closely mimic the situation in humans[18].

Accumulation of *C. albicans*-specific Th17 during commensalism depends on cognate antigen presentation and on Card9-dependent signals including IL-23[18,27], but overall remains not

well understood. The initiation and maintenance of the antifungal T cell response represent separate processes characterized by different signal requirements. Overall, the immunosurveillance response is uncoupled from inflammation, in line with the notion that inflammation is not compatible with homeostasis and consistent with what was also shown for the homeostatic T cell response against commensal bacteria[28]. 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[18]. This is reminiscent of the situation of other commensal- and virus-specific tissue-resident CD4+ T cells responses[29,30]. 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[31]. 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 cells that contribute to the overall IL-17 response for immunosurveillance of commensalism and homeostasis (Fig. 1A), although their identity and regulation remains to be defined in more detail.

C. albicans-specific Th17 cells act locally in the colonized tissue to keep homeostasis under control and prevent fungal

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[32]. Of note, the T cell response mounted in response to fungal colonization enhances resistance not only against the mycobiota itself but also against bacterial infections as shown in experimental models with C. difficile and C. rodentium[32,33].

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[34]. 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[34]. 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[35,36] including heterologous protection from systemic S. aureus[35]. Mechanistically, it was proposed that Th17 primed locally in the gut promote systemic neutrophil activation to enhance protection against an intravenous challenge[35]. Moreover, the mycobiota can impact physiological processes beyond host protection. As such, fungal gut colonization was recently proposed to promote social behaviour in mice[32]. The neuromodulatory role of mucosa-associated fungi occurs in an IL-17-dependent manner with neuronal cells acting as direct targets of IL-17[32]. This expands the previously noted effects of IL-17 on social behaviour[37–40] and provides a mechanistic basis for the reported associations of fungal dysbiosis and neuropsychiatric conditions in humans[41,42].

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[29]. 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 IL-10[43]. 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[44,45], where the inflammatory response is an acute and direct reaction to fungal virulence factors and release of keratinocyte-derived alarmins such as IL-1α[21], and is largely independently of the IL-17 pathway[45]. 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[46,47], and can be divided into five isotypes, which operate in distinct places and have distinct effector functions[48]. Antibody effector functions have classically been studied in the context of pathogenic infections[49]. However, it is apparent that luminal and serum antibodies bind members of the microbiota[50].

The fungal cell wall contains various pattern-associated molecular patterns (PAMPs), such as β-glucans, for innate immune recognition[51–54]. However, the C. albicans cell wall and secretory proteins are also a significant source of antigens[55]. 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[56]. 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[57]. Intestinal C. albicans colonization induces distal CSR and B cell expansion in germinal centers (GC) to induce high-affinity IgG. CSR and GC-B cell expansion is controlled by CARD9 and CX3CR1[+] mononuclear phagocytes (MNPs)[58]. Antifungal IgG responses are reduced in patients with polymorphisms in the coding region of the CX3CR1 or CARD9 genes[58,59], in whom CD has been described[60–63]. Furthermore, CARD9-deficient patients manifest fungal-specific infection susceptibility, predominantly in the central nervous system by C. albicans[64,65].

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[58]. IgG3 Abs are potent mediators of effector functions, including enhanced Ab-mediated cellular cytotoxicity, opsonophagocytosis, complement activation, and neutralization, compared with other IgG subclasses[66]. 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[58]. 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[58].

IgA is the dominant isotype at mucosal barriers[67], and predominantly induced in response to colonization with commensal organism to maintain homeostasis[68]. Within the mucosa, commensal microorganism are coated by low-affinity and antigen-specific secretory IgA (SIgA)[69]. Furthermore, IgA serves as the first line of defense in protecting the epithelium, from toxins or potential pathogenic microorganism overgrowth[68]. While immune exclusion is a dominant IgA effector mechanism[68], IgA is able to enchain pathogens, thereby preventing organism separation after replication resulting in clumping[70]. Accordingly, mucosal C. albicans colonization induces IgA[10–12] to reduce fungal-associated virulence attributes[11]. IgA binding to C. albicans prevents adhesion, invasion, and damage of epithelial cells[11,71] resulting in reduced inflammation[11]. In particular, IgA binds to hyphae-associated virulence factors, such as C. albicans adhesins or the toxin candidalysin[10,12]. 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[10–12]. Associated pathology is observed in patients with CD, in whom reduced virulence factor targeting SIgA have been described[10], and in NDV3 vaccinated mice, which generate IgA against the adhesion Als3 and have reduced pathology during DSS-induced colitis[12]. 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[72]. Oral mucosal C. albicans colonization increases CD19^{+} CD138^{−} B cell, plasmablast, and plasma cell enrichment in the

mucosa[11], while intestinal colonization increases the IgA$^+$ frequency and strong IgA CSR in the PP B cell compartment associated with high-affinity antibody responses[10]. These IgA responses are mediated through innate immune interaction with intestinal CD11c$^+$CD11b$^+$CD103$^+$ dendritic cells and CX3CR1$^+$ MNPs[10]. Trafficking of IgA ASCs is regulated by a combination of chemokine receptors as well as integrins[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[73]. 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[74].

SIgA can cross-react with a diverse fraction of the microbiota by canonical Fab-dependent and non-canonical carbohydrate-dependent binding[75]. Oral mucosal colonization with C. albicans increases total levels of cross-specific IgAs against the common oral commensal Streptococcus oralis[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[76]. 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[77], while secretion of IL-6 depends on hyphal stimulation and is mediated by MyD88[78].

Collectively, mucosal C. albicans colonization induces a variety of antibody responses, which not only restricts 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[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[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[20,85] and thereby represents rather an outlier than the norm within the species of C. albicans[20]. 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[11,20]. 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[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[86]. Moreover, because C. albicans actively masks PAMPS in response to its environment to reduce immune recognition[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[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[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[89]. Growth in the oral mucosa of mice selects for trisomy of chromosome 6, resulting in a commensal-like phenotype[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)[91]. C. albicans genomic and epigenetic variations can facilitate adaptation to environmental changes and improve the persistence of the fungus in various host niches[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[79–81]. 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.

IMMUNOPATHOLOGICAL CONSEQUENCES OF ADAPTIVE IMMUNITY AGAINST C. ALBICANS
While C. albicans is a common inhabitant of mucosal tissues in healthy individuals, fungal dysbiosis has been associated with diverse human diseases, including inflammatory disorders of colonized tissues such as gut, oral cavity, and skin, as well as pathologies in distant organs, including liver and lung. Whether and how the development and/or progression of pathology is causally linked with the observed shift in mycobiota composition remains often unclear and in many cases, the connection appears to be rather unspecific relying on innate mechanisms. However, several examples have recently emerged, where adaptive immune responses directed against C. albicans have been implicated in disease pathogenesis, comprising both T cell and antibody-mediated scenarios (Fig. 1B).

T cell-mediated immunopathologies
C. albicans (as well as other commensal fungi) are potent inducers of type-17 polarized responses, and IL-17 is implicated in the aetiology of many inflammatory disorders. As such, re-activation of mycobiota-specific Th17 cells can convey host-adverse effects and significantly aggravate tissue inflammation. In an experimental model of psoriasis, epicutaneous association of the murine skin with C. albicans was shown to exacerbates psoriaform skin inflammation in a Th17-dependent manner[93], in line with the observed enrichment of Candida-species in lesional skin of psoriasis patients[94] and the positive response of defined psoriatic patients to antifungals[95]. Similar results have been obtained with other skin commensal yeasts and in other models of skin inflammation[93,96].

Dysbiosis in Crohn's disease (CD) patients is characterized by an increase in C. albicans and other Candida species[97–102]. Accordingly, C. albicans-specific Th17 cells are increased in the blood of CD patients[14], presumably as a consequence of enhanced microbial translocation in the inflamed and barrier-disrupted gut, and their frequencies correlate with the faecal abundance of C. albicans in intensive care unit patients[35]. Most recently, the pathogenicity of gut-colonizing C. albicans isolates was identified

as a decisive factor for enhanced inflammation in IBD patients[103]. In light of the harmful rather than protective effects of IL-17 blockade in inflammatory bowel disease (IBD) patients[104], 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[105]. Alternatively, *C. albicans*-specific Th17 may exert host-protective effects in the inflamed gut, presumably via strengthening barrier repair functions[106] 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[3,59,107].

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[108]. Th17 cells are strongly expanded in the inflamed lung of chronic obstructive pulmonary disease (COPD) and asthma patients, which are frequently sensitized to *Aspergillus*[14]. In fact, Th17 cells responding to *A. fumigatus* also responded to *C. albicans*[14]. 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[109]. 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[110]. 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[14]. Antigen-specificity is a key hallmark of adaptive immunity. Only a few fungal antigens have been identified so far[14,15,111]. 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*[14]. 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 mycobiota 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[10,112]. 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[113]. Mannans from other yeasts, such as *C. albicans*[114], can cross-react with ASCA suggesting that other yeast may induce ASCA-associated diseases[115]. In fact, in a mouse model of dextran sodium sulfate (DSS)-induced colitis *C. albicans* colonization generates ASCA and promotes inflammation[116]. In this context, systemic ASCA develops consistently in patients with CD[117,118], in whom fungal dysbiosis and overgrowth of *Candida* species have been described[101,119]. Furthermore, an increase in *Candida* abundance and serum ASCA generation was shown in patients with alcohol-associated liver disease[120,121]. ASCA levels correlated with disease severity and increased mortality[122], and were reversed upon 2 weeks of alcohol abstinence[120]. Similarly, anti-*C. albicans* antibodies were also elevated in non-alcoholic fatty liver disease patients and correlated with the degree of fibrosis[123]. Antifungal therapy prevented ethanol-induced liver disease in mice[121], 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[124]. 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[125]. High antibodies titers against IL-17A, IL-17F, and IL-22 can be found in patients with CMC and autoimmune polyendocrine syndrome type I[126,127]. However, some patients with persistent IL-17 auto-Abs lack CMC, and some patients with CMC lack auto-Abs[128,129] 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[34,130].

VACCINES AGAINST *C. ALBICANS*

Vaccines are among the most successful public health interventions[131] 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[132], that this fungus is a lifelong inhabitant of mucosal surfaces[133], and every colonized individual harbour a memory response directed against *C. albicans*[10,12–14], 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[6,134,135] 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[136], IgG, and IgA[12,137] responses in mice and humans. NDV-3 vaccinated mice are protected against systemic and mucosal *C. albicans* infection[136,138–140], while inducing cross-reactive protective responses against *C. auris* and *Staphylococcus aureus* in mice[136,141]. Furthermore, NDV-3 vaccination prevents *C. albicans*-associated damage in mice with colitis by inducing fungal adhesin-specific IgA responses[12]. Importantly, NDV-3 has been shown to be safe and efficacious in a clinical trial against recurrent vulvovaginal candidiasis[142]. A different study uses the recombinant *C. albicans* secreted aspartyl proteinase 2 (Sap2) protein[143]. Sap2 plays an important role in fungal pathogenesis by degrading host proteins at mucosal sites and inactivate complement components[144–146]. Vaccination with Sap2 results in the generation of antigen specific protective antibodies[147], which cross-react with different members of the Sap family[148]. 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 have 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[149,150], human immunological research is advancing disease treatment while also generating insights into basic immunological concepts[151]. This has led to exciting discoveries regarding the relevance and role of adaptive immunity in immuosurveillance of *C. albicans* commensalism, 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, Lionakis 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[34]. Thus, studying tissues directly will aid our understanding of tissue-resident cell types (such as resident memory lymphocytes and tissue-specific stroma) and inform 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[20,84] should be used to closely mimic scenarios seen in patients.

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AUTHOR CONTRIBUTIONS

Both authors contributed equally to the preparation of this review article.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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