REVIEW

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Adaptive immune responses to *Candida albicans* infection

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Fungal infections are becoming increasingly prevalent in the human population and contribute to morbidity and mortality in healthy and immunocompromised individuals respectively. *Candida albicans* is the most commonly encountered fungal pathogen of humans, and is frequently found on the mucosal surfaces of the body. Host defense against *C. albicans* is dependent upon a finely tuned implementation of innate and adaptive immune responses, enabling the host to neutralise the invading fungus. Central to this protection are the adaptive Th1 and Th17 cellular responses, which are considered paramount to successful immune defense against *C. albicans* infections, and enable tissue homeostasis to be maintained in the presence of colonising fungi. This review will highlight the recent advances in our understanding of adaptive immunity to *Candida albicans* infections.

Introduction

The human body is a complex environment which is colonised both internally and externally by a huge number of different microbial species including bacteria, fungi and viruses. The maintenance of tissue homeostasis in the face of such overwhelming microbial diversity is critical to health and is dependent upon effective immune surveillance. *Candida albicans* is a polymorphic fungus found in the digestive tract and on other mucosal surfaces of the body (e.g. oral cavity and vagina). The fungus is considered to be a normal constituent of the microflora in ~50% of the human population[1] and is the cause of superficial mucosal infections such as oral and vaginal thrush which can occur following perturbations in the localized mucosal environment. *C. albicans* is also capable of causing life threatening illness and accounts for significant rates of mortality (40%) in the immunocompromised and those receiving immunosuppressive therapies.[2] The dichotomy between harmless carriage and the onset of potentially life threatening infection stems from 2 critically important factors, namely the presence or absence of an effective immune response and the ability of the fungus to alter its morphology.

C. albicans can grow in a number of distinct physical forms including unicellular yeast, pseudohyphae and hyphae.[1] The morphological transition(s) which occur during growth are reversible,[3-5] and such physical plasticity is believed to facilitate pathogenicity. Growth of *C. albicans* as unicellular yeast is typically associated with harmless colonisation (commensalism) whereas pseudohyphal and hyphal growth is more closely associated with infection. However, it is important to emphasize that this mutually exclusive view of morphology during health or disease is somewhat oversimplified, and may not accurately reflect the true situation during clinical pathogenesis where multiple morphologies are often encountered simultaneously. While infections of the mucosal surfaces are predominantly associated with the hyphal form of the fungus, widespread dissemination throughout the body is facilitated by the yeast morphology where cells bud-off from pre-established hyphae and transit to remote tissues and organs such as the kidneys.

A complex and dynamic relationship exists between *C. albicans* and the human host, the balance of which is influenced greatly by the immune system. Indeed, the pathogenic potential of *C. albicans* is primarily determined by the effectiveness of the host immune response. A state of relative co-existence is maintained between host and fungus in healthy individuals, whereby growth is restricted to the harmless commensal form. However, the morphological restrictions imposed upon fungal growth during health are removed in the absence of effective immune surveillance, which allow fungal burdens to increase as growth continues unchecked. The hyphae of *C. albicans* can breach mucosal surfaces causing infection. Hyphal growth causes damage to the underlying tissue and if it progresses to the point where access to the host vasculature is enabled, the fungus can disseminate throughout the body. Furthermore, many fungal infections also result from the use of indwelling medical devices including intravenous lines, catheters and drains, which bypass the physical barrier provided by the mucosal surface, facilitating access to the bloodstream. Such deep-seated systemic infections are a significant threat to life, and patients suffering from HIV/AIDS and those receiving immunosuppressive therapy are particularly susceptible.

Defense against microbial infection is provided by an exquisite interplay between the innate and adaptive arms of the host immune system which function together to eliminate pathogens from the body. In this review we will summarise the basic features of the adaptive immune response to *C. albicans* infection,

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describing recent advances in our understanding of adaptive immunity to this medically important fungus.

Host Recognition of *Candida albicans*: Dendritic Cells

Dendritic cells (DCs) are specialized antigen presenting cells (APCs) that play a central role in immune defense against pathogens, serving as a critical conduit between the innate and adaptive immune responses. DCs are vital for the initiation of adaptive T-cell-mediated immune protection against *C. albicans*. Immature DCs patrol the peripheral tissues beneath mucosal surfaces and are recruited to the site of infection in response to chemokines and antimicrobial peptides (e.g., CCL20[6-8] and β-defensin 2[9,10] respectively), secreted by epithelial cells in response to microbial infection. Once recruited, recognition of *C. albicans* by DCs occurs through interactions between pattern recognition receptors (PRRs) expressed on the surface of the DC and pathogen-associated molecular patterns (PAMPs) present on the fungal cell wall.[11]

PRRs including C-type lectin receptors (CLRs)[12] such as dectin-1, dectin-2 and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), mannose receptor (MR), Mincle, Galectin-3, toll-like receptors (TLRs)[13] (such as TLR2 and TLR4), and complement receptor 3 (CR3) have all been associated with recognition of fungi. PRRs involved in fungal detection recognize conserved structural motifs present as part of the fungal cell wall, such as *N*-linked[14] and *O*-linked mannans and β-glucans.[15] Although this initial interaction between host and fungus is driven primarily through innate rather than adaptive recognition, it is nevertheless a crucial event required for the initiation of an adaptive immune response. Once detected, the fungal cells are phagocytosed by DCs and degraded,[16] providing a source of exogenous protein which is processed into antigenic peptides within acidified vesicles. These fungal peptide antigens are assembled onto class II molecules of the major histocompatibility complex (MHC II) and subsequently transported to the surface of the activated DC. Acquired fungal antigens are presented to memory T-cells present in the local environment, and this process is accompanied by the migration of the DCs to the draining lymph nodes, where the antigens are presented to naive T-lymphocytes.

Interestingly, the activation of DCs during *C. albicans* infection results in different antigen-specific immune responses. Presentation of *C. albicans* antigens by Langerhans cells is required to elicit Th17 responses but does not promote the development of $CD8^+$ cytotoxic T-lymphocyte (CTL) responses.[17] In contrast, $Langerin^+$ dermal DCs stimulate both Th1 and CTL responses while simultaneously inhibiting the development of the Th17 response. Induction of a CTL response indicates that antigens derived from phagocytosis of fungal cells were cross-presented through the MHC I pathway for display to $CD8^+$ T-lymphocytes. Thus, mixed populations of DCs have non-redundant functionality and can drive $CD4^+$ and $CD8^+$ T-cell responses against *C. albicans*.

T-lymphocytes sample the antigen presented to them using T-cell receptors (TCRs) expressed on their surface. Specificity to a potentially unlimited number of antigenic molecules is enabled by random variations in the amino acid sequence (and hence structure) of the antigen binding region of the TCR. Binding of the TCR to either MHC I or MHC II molecules displaying processed fungal antigen is facilitated by the expression of the co-receptors $CD8^+$ and $CD4^+$ respectively, and authenticated though interactions between CD28 expressed on the T-cell and CD80/CD86 on the APC. Recognition of antigen is accompanied by the secretion of cytokines which drive the activation and differentiation of the naive T-lymphocyte into one of a number of different possible T-helper (Th) subsets.

Signaling Events in DCs that Drive Th Subset Differentiation

The recognition of PAMPs by PRRs results in the activation of signaling pathways within the DC which ultimately results in the induction of a specific adaptive cellular immune response. The signaling events that transpire following fungal recognition by the DC and the induction of cellular immunity are both dynamic and complex, and have yet to be characterized in full.

The CLR dectin-1 is expressed on the surface of APCs and plays a central role in the orchestration of responses to *C. albicans*. Dectin-1 is comprised of an extracellular carbohydrate recognition domain and a partial immunoreceptor tyrosine-based activation (ITAM) motif and is the receptor for fungal cell wall β-glucan.[18] The recognition of fungal β-glucan by dectin-1 triggers receptor activation through phosphorylation of the cytoplasmic domain[19,20] which in turn leads to recruitment and activation of the spleen tyrosine kinase (SYK)[21] (**Fig. 1A**). Association of phosphorylated dectin-1 with Syk triggers the assembly of the caspase recruitment domain (CARD) complex consisting of CARD9, Bcl-10 and MALT1.[19,20,22] The importance of this process in adaptive immune responses to *C. albicans* can be demonstrated as $CARD9^{-/-}$ mice are unable to mount Th17 responses to oral infection.[23]

Assembly of the CARD complex leads to activation of the IκB kinase complex which promotes activation and nuclear translocation of the transcription factor NF-κB[22] (**Fig. 1 B**). Gene transcription mediated via NF-κB signaling results in secretion of pro-inflammatory cytokines and the concomitant upregulation of co-stimulatory molecules on the APC surface (**Fig. 1 D**), the net effect being the induction and differentiation of naive T-cells into distinct Th lineages (Th1, Th2, Th17, Treg). In addition to the "classical" signaling mediated through Syk and p65, dectin-1 can also signal through the non-cannonical NF-κB subunit RelB and importantly, through a second, Syk-independent pathway dependent upon Raf-1[24]. All these pathways converge on NF-κB to drive Th1 and Th17 polarization, and subsequent adaptive immunity against *C. albicans.*[24]

Other CLRs have also been reported as playing a role in driving adaptive immune responses to *C. albicans*, including dectin-2.[25] However in contrast to dectin-1 which, during canonical

signaling, interacts with Syk directly, dectin-2 induces signaling through Syk indirectly by association with the FcRγ chain.[26] Blockade of dectin-2 expressed on DCs has been reported to reduce Th17 responses during systemic infection with *C. albicans*.[25]

T-cell Responses to *Candida albicans*

T-lymphocytes (T-cells) are an integral component of the host adaptive immune response to *C. albicans* infection and provide direct and indirect means of controlling fungal proliferation. Both $CD4^+$ (T helper cells) and $CD8^+$ (CTL) T-cells have been shown to play a role in anti-fungal immunity, and their activation is controlled by dendritic cell populations. Although CTLs have been shown to inhibit the growth of *C. albicans* hyphae *in vitro*,[27] the principal mechanism of adaptive immune priming employed by DCs occurs through the presentation of fungal antigen to naive $CD4^+$ T-cells, generating a T-helper (Th) response. The $CD4^+$ Th cell response is the predominant cell-mediated adaptive immune response to *C. albicans* infection at mucosal surfaces. Unlike CTLs, $CD4^+$ T-cells do not possess direct cytolytic activity but nevertheless play a crucial role in the cellular adaptive response to fungal infection. The importance of the Th cellular response in driving protective immunity against *C. albicans* is highlighted by the prevalence of oropharangeal candidiasis (OPC) in HIV^+/AIDS patients where the $CD4^+$ T-cell count is depleted.[28,29] Indeed, the correlation between HIV/AIDS and *C. albicans* infection in the oral cavity is now such that the presence of OPC is now widely regarded as a reliable predictor of low $CD4^+$ cell count.[28,29]

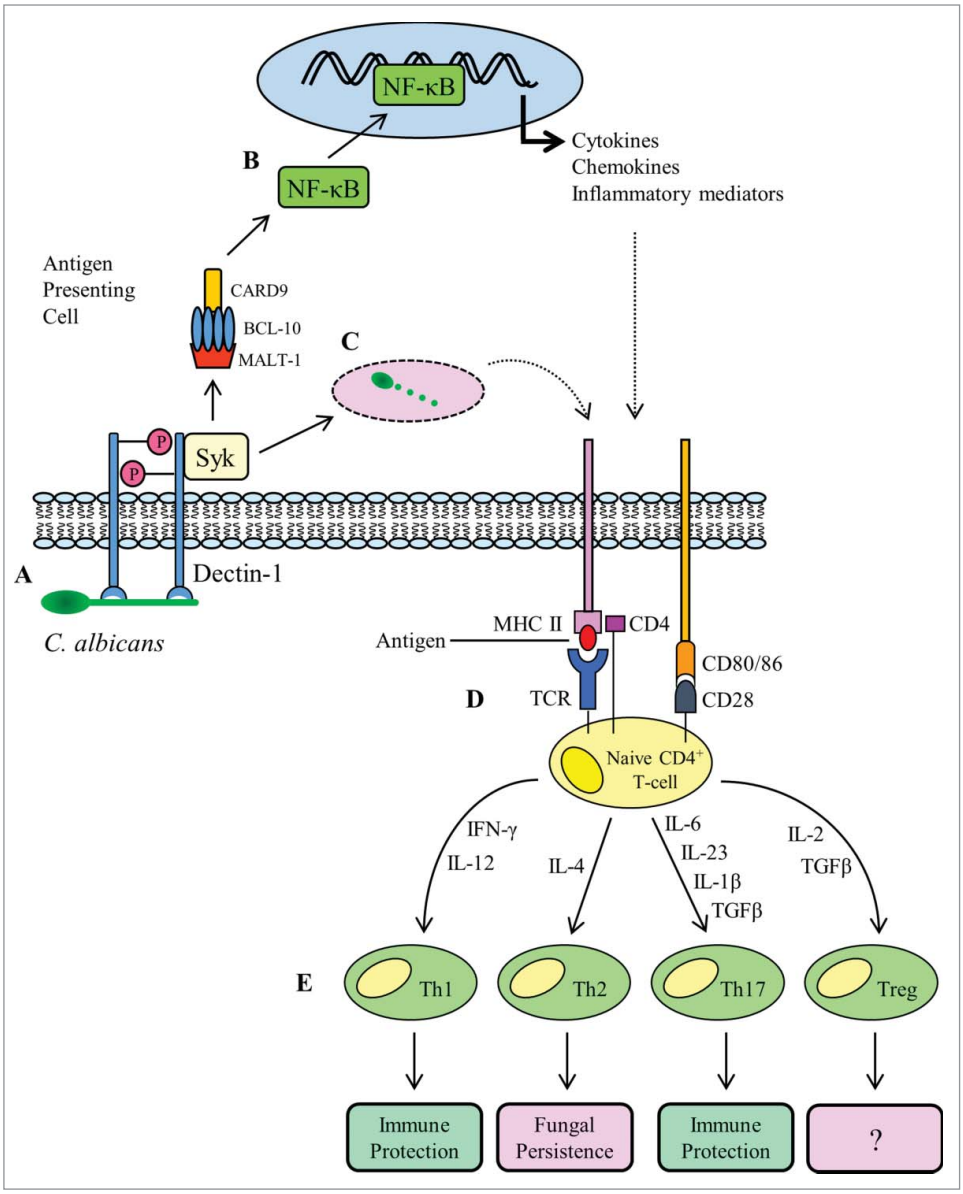

Figure 1. Overview of adaptive T-cell responses to *Candida albicans* infection. A fungal PAMP (β-glucan) engages with the PRR dectin-1 (**A**), stimulating receptor phosphorylation and recruitment of the spleen tyrosine kinase (SYK). The association of dectin-1 with SYK activates assembly of the CARD complex (CARD9, BCL-10 and MALT-1), which stimulates nuclear translocation of the transcription factor NF-κB (**B**). The NF-κB transcription factor drives the expression of pro-inflammatory cytokines and co-stimulatory molecules required during antigen presentation. As well as signaling and gene transcription, activation of dectin-1 and recruitment of SYK triggers phagocytosis of *C. albicans* (**C**). The phagocytosed fungus is degraded in the phagocytic compartment and fungal antigens are loaded onto MHC II molecules for presentation to naive $CD4^+$ T-cells. Recognition of antigen by a T-cell receptor (TCR) in the presence of co-stimulation from CD28 and CD80/86 (**D**) is followed by cytokine-directed polarization to one of the 4 known Th subsets (**E**). Th1 and Th17 cellular responses confer immune protection, whereas Th2 responses are considered refractory to fungal clearance.

There are 4 different Th subsets (Th1, Th2, Th17 and Treg), and the development of each specific subset is dictated by the cytokines and microenvironment present at the instance of naive $CD4^+$ T-cell priming by DCs. The cytokines that drive the differentiation of each particular Th phenotype are inhibitory to the development of the others, thereby maximising the potential that only one type of Th response is initiated at any one time. This so called "polarization" of Th differentiation has a profound impact on the outcome of the adaptive response and is heavily dependent upon the prevailing cytokine milieu. Th1 responses were

historically regarded as being the predominant defensive cellular response to *C. albicans*, resulting in fungal clearance from the oral cavity and gastrointestinal tract. However, this view of the importance and effective contribution of the Th1 phenotype to protection against *C. albicans* infection at mucosal surfaces has since been superseded by the Th17 response. In contrast to the protective Th17/Th1 phenotypes, induction of a Th2 phenotype is more closely associated with increased growth and dissemination of the fungus.

DCs that phagocytose *C. albicans* yeast cells are stimulated to produce interleukin-12 (IL-12), which drives polarization to the Th1 subset. Upon stimulation with IL-12, Th1 cells initiate autocrine signaling via secretion of interferon-gamma (IFN-γ) which serves to upregulate the expression of the IL-12Rβ2 receptor rendering the cells increasingly sensitive to IL-12 stimulation, thereby perpetuating differentiation to the Th1 phenotype.[30] In contrast, polarization to the Th2 phenotype is driven by IL-4 and is accompanied by further secretion of IL-4.

IL-17 secreting T-lymphocytes (Th17 cells) are an additional subset of Th cell which express the chemokine receptors CCR4 and CCR6 on their surface[31] and are developmentally distinct from the Th1 and Th2 lineages.[32] Th17 cells secrete numerous cytokines including IL-17A, IL-17F and IL-22 and are critically important for immune protection against *C. albicans* at the majority of mucosal sites in the body. Indeed, such is the involvement of Th17 cells in the immune response to oral and dermal candidiasis they are now regarded as the predominant cell type that confer protection against *C. albicans* at these locations.[33,34] Interestingly, IL-17 and IL-22 do not contribute to immune protection in vaginal mucosa,[35] highlighting the subtle differences in immune response requirements at different mucosal sites.[33,34] IL-17 plays a key role in recruiting and activating neutrophils,[36] while IL-22 enhances epithelial barrier function.[37] Differentiation of naive $CD4^+$ T-cells to the Th17 phenotype is driven initially by IL-1β,[38,39] while maturation and terminal differentiation is dependent upon IL-23 signaling.[40] Th17 differentiation is further influenced by IL-6, which has been shown to be produced by epithelial cells in response to *C. albicans* infection.[41] Notably, the production of both IL-6 and IL-23 from antigen presenting cells results from recognition of *C. albicans* mannan.[42]

More recently, an additional class of natural Th17 (nTh17) cells have been described that are phenotypically distinct from conventional $CD4^+$ Th17 cells.[43-45] nTh17 cells function as innate sentinels in the oral mucosa and together with γδ T cells, secrete IL-17 in response to *C. albicans.*[45] Notably, γδ T cells produce large quantities of IL-17,[45] yet again highlighting the close relationship between innate recognition of *C. albicans* and downstream adaptive immune responses. It is also important when considering immune responses to *C. albicans* to be aware that many of the cytokines now thought to be important in these responses (e.g. IL-17A, IL-22) can also be produced by innate lymphoid cells (ILCs) such as the aforementioned nTh17 cells, γδ T cells, as well as ILC3 cells. Further, many of the *in vivo* models of mucosal *C. albicans* infection are skewed toward assaying innate rather than adaptive immune responses given the timescales over which these models are carried out.

The importance of the Th17 phenotype cytokines in anti-*Candida* responses is most vividly portrayed by data from both knockout mice and human patients. Mice unable to produce IL-23 are highly susceptible to OPC,[46] while mice lacking IL-17 receptor-A ($IL\text{-}17RA^{-/-}$) or IL-23p19 ($IL\text{-}23p19^{-/-}$) have increased susceptibility to both OPC and systemic candidiasis.[36,47] Moreover, $IL\text{-}17RC^{-/-}$ mice (deficient in the second IL-17 receptor chain) are also susceptible to OPC.[48] Both IL-17 and IL-23 are essential in preventing fungal skin infections[33] and Th17 cells secrete IL-22 which limits fungal growth.[37]

In addition to acquired disorders of $CD4^+$ T-cell immunity that predispose to *C. albicans* infection (HIV/AIDS), the critical nature of the protection provided by IL-17/Th17 cells is further emphasized when one considers the impact of inherited genetic mutations which affect the efficacy of IL-17/Th17 responses in otherwise healthy individuals.

Patients with inherited disorders in Th17-mediated anti-fungal immunity frequently present with chronic mucocutaneous candidiasis (CMC), which manifests as severe infection of the nails, skin and upper gastrointestinal tract. IL-12 and IL-23 are important cytokines for the development of Th1 and Th17 responses respectively. The human IL12RB1 gene encodes for an integral component of the receptor to IL-12 and IL-23, and approximately 25% of patients deficient in IL-12Rβ1 are prone to CMC.[49,50] In patients with autosomal dominant Hyper-IgE syndrome, the differentiation, development and number of circulating Th17 cells is significantly reduced[51-53] due to mutations in Signal Transducer and Activator of Transcription 3 (STAT3), and CMC is a key phenotype in these individuals.[54,55] Further, Th17 development and associated anti-fungal activity is also impaired by gain-of-function mutations in STAT1.[56]

A marked reduction in the number of IL-17 secreting T-cells is observed in patients carrying the dominant-negative autosomal recessive Q258X mutation in caspase recruiting domain-containing protein 9 (CARD9)[57] and this mutation has been associated with increased susceptibility to fungal infection.[58] Furthermore, individuals with autosomal recessive autoimmune polyendocrinopathy syndrome 1 (APS-1), caused by mutations in the gene encoding the human autoimmune regulator protein (AIRE)[59,60] produce neutralising antibodies against IL-17A, IL-17F and IL-22. The continual depletion of these key Th17 cytokines results in an associated CMC.[61,62] Importantly, the susceptibility of APS-1 patients to opportunistic pathogens is seemingly restricted to *C. albicans* alone, highlighting the specific and essential contribution of IL-17 to anti-*C. albicans* immunity. Moreover, both an autosomal recessive mutation of glutamine 284 to a premature termination codon in the receptor for IL-17A (IL-17 RA) and an autosomal dominant mutation (S65L) in IL-17F also predispose individuals to CMC.[63] A T536I mis-sense mutation in ACT1 (an adaptor protein involved in IL-17 signaling) is reported to reduce activity and impaired IL-17A and IL-17F-mediated immunity. Patients harbouring the ACT1 mutation have T-cells which are unresponsive to IL-17E and an increased prevalence of CMC.[64]

One of the classical hallmarks of adaptive immunity is the establishment of permanent immunological memory against a specific antigen, which can be brought to bear against a pathogen

in the face of a secondary immune challenge. Long-term adaptive immunity against *C. albicans* has been observed in mice challenged and then re-challenged with the fungus. In this system, a stable and robust antigen-specific adaptive Th17 immune response against *C. albicans* was reported,[34] but the establishment of *bona fide* immunological memory remains to be fully demonstrated. Taken collectively, these studies clearly demonstrate the essential role that Th17 cells, their associated cytokines and by extension, adaptive immunity, play in combating *C. albicans* infections.

Antibody Responses to *Candida albicans*

Endogenous antibody responses to *C. albicans* infection in humans are regarded as playing a relatively minor role in immune protection against the fungus, and are widely considered to be significantly less effective than cellular (Th17/Th1) responses. Due to their accessibility, molecules displayed on the cell surface of *C. albicans* provide ideal targets for antibody-mediated immune protection. Mannoproteins with complex *O*- and *N*-linked mannose polysaccharides are an integral component of the *C. albicans* cell wall[65] and are a major target for anti-*Candida* antibodies. The binding of antibodies to exposed cell surface components of the infecting fungus may serve to hinder or prevent biological function. Indeed, monoclonal antibodies generated against mannoprotein interfere with fungal adhesion to host substrates and germ tube formation,[66] while patient-derived antibodies against a 58 kDa cell surface mannoprotein of the fungus prolonged survival following systemic infection in mice.[67]

Antibodies generated in mice against the surface mannan of *C. albicans* can confer varying degrees of protection, depending upon whether the subsequent fungal infection is mucosal or systemic.[68] Vaccination with *C. albicans* mannan rendered mice less susceptible to disseminated candidiasis and polyclonal serum from vaccinated animals conferred protection to both naive mice and those with severe combined immune-deficiency (SCID).[69] Administration of a recombinant human monoclonal antibody against *C. albicans* mannan to mice enabled prolonged survival following an otherwise lethal inoculum of the fungus.[70]

The agglutinin-like sequence proteins of *C. albicans* also reside at the cell surface, and monoclonal antibodies which bind to Als3p interfere with adhesion to epithelial surfaces, filamentation, acquisition of iron, and also possess fungicidal activity.[71,72] Interestingly, antibody-mediated protection against *C. albicans* is not restricted to cell surface molecules alone. Antibody-mediated inhibition of secreted aspartyl proteinase (SAP) activity was reported to bestow increased protection against vaginal infection in rats,[73] while human antibodies specific for *C. albicans* heat shock protein 90 (Hsp90) protected against systemic candidiasis in mice.[74]

Despite these observations, there is the paradox that B-cell deficiency in mice does not cause increased susceptibility to *C. albicans* infection,[75-77] highlighting the lack of robust antibody-mediated protection and emphasizing the predominance of adaptive cellular responses.

Given the extremely modest levels of protection conferred by antibodies in response to *C. albicans* infection, it could be argued that the inherent immunogenicity of *C. albicans* antigens is limited in their natural context when presented to B-cells. However, it is also clear that purified antigens, when presented to the immune system in conjunction with a suitable carrier protein and adjuvant are capable of eliciting the production of antigen-specific antibodies that can confer some, albeit limited, protection (see Vaccines to *Candida albicans*).

Subversion of adaptive immune responses by *Candida albicans*

As with most pathogens, *C. albicans* has developed mechanisms for avoiding immune responses. This can include evasion of recognition events or even subversion of normal immune responses. The mechanisms by which *C. albicans* manages this are varied. For example, the cellular immune response driven during infection can be influenced by fungal morphology. Monocytes that phagocytose *C. albicans* yeast cells or germ tubes were unable to differentiate into DCs, and internalisation of germ tubes was reported to render cells incapable of inducing Th polarization.[78] Further, the yeast and hyphal forms of *C. albicans* exert opposing effects on DCs, skewing Th polarization induced both *in vitro* and *in vivo*.[79,80] Such a polarization of the cytokine response may function to subvert Th subset differentiation to those which enable fungal persistence within the host. DCs which phagocytose *C. albicans* yeast cells or those pulsed with yeast cell RNA promote development of Th1 responses, leading to fungal clearance, whereas DCs that internalise hyphae or those which receive hyphal RNA generate Th2 responses leading to fungal perpetuation.[79,80] Importantly, DCs pulsed *ex vivo* with yeast but not hyphae were reported to confer anti-fungal protection when adoptively transferred into mice.[79] In addition to morphological influences, *C. albicans* can secrete a soluble factor which reduces IL-17 production from human peripheral blood mononuclear cells *in vitro,*[81] suggesting that the fungus may have the potential to dampen host Th17 responses. Furthermore, it has also been suggested that the presence of IL-17A may facilitate fungal adaptation to the host environment.[82]

T-regulatory (Treg) cells are known to play a central role in the regulation of cellular immune responses to microbial infection. The induction of disseminated candidiasis in mice was reported to drive the expansion of a population of splenic $Foxp3^+$ Treg cells resulting in the exacerbation of disease pathology. Interestingly, subsets of $Foxp3^+$ Treg cells were observed to induce Th17 responses, albeit to the detriment of the host.[83] In contrast to these findings is the observation that Treg cells consume IL-2 (thereby preventing IL-2-mediated inhibition of Th17 polarization), assisting the generation of protective Th17 responses mounted during murine OPC.[84] Clearly, the roles(s) played by Treg cells in response to *C. albicans* infection have yet to be characterized in full.

Taken together it appears probable, whether intentional or otherwise, that *C. albicans* is able to influence the outcome of the

host immune response in some circumstances, possibly to circumvent immune clearance and facilitate persistence.

The role of the inflammasome in the adaptive immune response to *Candida albicans*

The complex interplay between innate and adaptive immune responses that enables fungal clearance is further demonstrated by the involvement of the inflammasome in response to fungal challenge. Inflammasomes are cytosolic multi-protein complexes consisting of a PRR, an adaptor protein (e.g., ASC) and caspase-1, whose assembly is triggered via innate recognition of PAMPs by intracellular nucleotide-binding domain and leucine-rich repeat-containing (NLR) proteins or AIM2-like receptors (ALRs).[85] It is becoming increasingly clear that these structures play an important functional role in the adaptive immune response to fungal infection. The end point of inflammasome activation is the production of fully mature inflammatory cytokines IL-1β and IL-18. IL-1β and IL-18 are produced as inactive precursors that undergo caspase-mediated cleavage to yield biologically active molecules. Inflammasome activity is required to drive caspase-dependent maturation of IL-1β and IL-18, with subsequent effects on adaptive Th1 and Th17 cellular responses.[38,86,87] Accordingly, while the initiation of inflammasome activity is associated with innate immunity, the production of functionally mature IL-1β and IL-18 nevertheless influence the outcome of the adaptive immune response.

A number of different inflammasomes are known to be involved in the response to *C. albicans* infection. By far the best characterized of these is the NLRP3 inflammasome which consists of Nlrp3 complexed with apoptosis-associated speck-like protein with caspase recruitment domain (ASC) and caspase-1. The ability to produce mature IL-1β and IL-18 through the NLRP3 inflammasome is crucial for adaptive cellular protection against *C. albicans*. Activation of the NLRP3 inflammasome is triggered by *C. albicans* hyphae,[88] and has an impact in signaling through other PRRs involved in anti-*Candida* immunity. For example, NLRP3/ASC caspase-1 activity is a critical factor in SYK/CARD9 signaling induced by TLR2 and dectin-1.[89,90] Further, secretion of IL-1β from DCs stimulated with fungal β-glucan required NLRP3 inflammasome activity and cells deficient in either Nlrp3 or ASC were impaired in their ability to secrete IL-1β.[91] The importance of the NLRP3 inflammasome in anti-*Candida* responses can be seen in studies using knock-out mice. Mice lacking in either TLR2, dectin-1, caspase-1 or Nlrp3 are highly susceptible to systemic *C. albicans* infection,[88-90] while mice unable to produce caspase-1 or ASC were more susceptible to disseminated candidiasis and exhibited reduced Th1/Th17 reactivity concomitant with increased fungal burden in the kidneys.[92] These inflammasome effects are important for more than cell-mediated immunity, with studies showing that NLRP3 activity was required for the generation of antigen-specific antibody mediated immune protection against *C. albicans in vivo*.[91] In addition to NLRP3-mediated protection, immune defense against *C. albicans* infection can also be orchestrated through the NLRC4 inflammasome which functions to regulate resistance to infection in the oral cavity and limits early systemic dissemination following oral infection *in vivo*.[93]

NLRP10 is another member of the NLR family which contributes to adaptive immune protection against disseminated candidiasis *in vivo*[94] and is expressed on DCs and $CD4^+$, but not $CD8^+$ T-cells. Mice lacking NLRP10 exhibited impaired Th1 and Th17 responses to *C. albicans* infection concomitant with an increased presence of both yeast and hyphae in the renal cortex and medulla.[94] Importantly, while adaptive cellular responses were negatively affected by the absence of NLRP10, activation of the NLRP3 inflammasome and secretion of IL-1β were not affected, indicating that while both NLRP3 and NLRP10 contribute to adaptive protection against *C. albicans* infection, they do so by different pathways.[94] As can be seen, the exact role of inflammasome activation in adaptive immune responses is difficult to isolate, given the parallel role these complexes play in innate immunity. The reality is likely to be a multifaceted interplay between the different inflammasome complexes and fungal PAMPs, resulting in complementary activation of both innate and adaptive immunity. It should be noted that the cytokine cocktail produced by inflammasome activity (IL-1β and IL-18) will help drive the development of a Th17 phenotype in naïve T-cells, thus the innate immune activation of inflammasomes can still have an impact on adaptive immune responses.

Since NLRs are intracellular receptors, the activation of inflammasome assembly typically proceeds following phagocytosis/internalisation of the infecting fungus. However, recognition of *C. albicans* by DCs expressing the extracellular PRR dectin-1 can also trigger the assembly of a non-canonical inflammasome complex consisting of CARD9, Bcl-10, MALT1, ASC and caspase-8, rather than caspase-1[95]. Assembly of this multi-protein complex enables processing of inactive IL-1β to the active form in a caspase-8 dependent manner. Intriguingly, while activation of the NLRP3/caspase-1 inflammasome by *C. albicans* is dependent upon internalisation of the fungus, blocking the internalisation of *C. albicans* does not affect caspase-8-dependent maturation of IL-1β from the non-canonical inflammasome complex.[95] Hence, induction of protective Th17-based immunity against *C. albicans* can be triggered following intracellular and extracellular recognition of the fungus in a manner dependent upon the activity of classical and non-canonical inflammasomes respectively.

Compartmentalisation of Immunity

C. albicans is known to infect multiple mucosal sites including the oral and vaginal cavities in particular. Each of these surfaces has their own immune mechanisms and susceptibilities to infection. For example, while oral thrush is generally associated with significant underlying changes, such as denture use or immune deficiencies (AIDS, transplantation therapy, cancer treatments), vulvovaginal candidiasis (VVC) is a much more common occurrence in the general population. Indeed, ~75% of women of fertile age will experience at least one incidence of VVC[96,97] and it has been estimated that 5–10% of women will suffer from

repeated or chronic episodes of VVC.[98,99] It is therefore highly likely that there are differences in the immunity generated at each of these different sites. Interestingly, adaptive Th17 responses appear to play no role in vaginal protection to *C. albicans*, with no change in the vaginal fungal burden of IL-23p19$^{-/-}$, IL-17RA$^{-/-}$ and IL-22$^{-/-}$ mice compared with wild type controls.[100] This highlights the fact that although there are common anti-fungal mucosal immune responses, it is also highly likely that there is a varying degree of specificity for each of these mucosal surfaces to the fungus. In particular, it is noteworthy that responses to systemic infection differ from responses at mucosal surfaces. Systemic responses for example, are still regarded as being predominantly Th1, while mucosal responses are now known to be predominantly Th17 in nature.

The contribution of adaptive immune responses against *C. albicans* during vaginal infection remains somewhat unclear. Despite participating in adaptive immune protection at a number of different sites in the body,[101-103] Th1 cells play no significant role in protection against *C. albicans* in the vaginal environment,[104] and a precise biological role for this so called "compartmentalisation of immunity" has yet to be unequivocally established.

In an experimental model of VVC, DCs were detected in the draining lymph nodes of the surrounding vaginal tissue. However, the predominant subset of DC found within the nodes were plasmacytoid dendritic cells (pDCs),[105] which are associated with immunological tolerance and poor induction of T-cell proliferation,[106] rather than myeloid DCs which promote inflammatory responses and fungal clearance. Importantly, the pDCs were detected prior to, and throughout the entire course of infection and did not upregulate expression of MHC II, CD80 or CD86,[105] consistent with a localized, tissue-specific tolerance to the fungus.

The involvement of Th17 responses to *C. albicans* infection in the vagina have yet to be fully elucidated. Induction of VVC in mice stimulated the production of both IL-17 and IL-23, together with a potent influx of neutrophils.[107] However, despite the role played by IL-17/Th17 in driving neutrophil recruitment to the sites of infection, the presence of neutrophils was ineffectual and the severity of infection was not diminished.[107] Interestingly, the secretion of IL-17 was noted to influence the production of the anti-microbial peptides β-defensin 2 and β-defensin 3. Reducing the level of IL-17 exacerbated VVC severity while simultaneously reducing the level of β-defensin 2, whereas production of β-defensin 2 was increased following addition of recombinant IL-17.[107]

In contrast to the above study, recruitment of neutrophils during vaginal infection was observed in response to the presence of S100A8 and S100A9 alarmins,[35] and no role for the involvement of either IL-17 or the Th17 pathway was demonstrated.[100] Given the involvement of the S100 alarmins and β-defensins, defense against *C. albicans* in the vaginal environment thus appears to be mediated through innate rather than adaptive means in murine models of VVC. Indeed, the PRRs TLR4 and SIGNR1 have been implicated in S100 alarmin signaling *in vitro*, although the situation appears to be more complex *in vivo.*[108] Importantly, and in keeping with the observations made above, the symptoms caused by intravaginal challenge with live, unattenuated *C. albicans* in human subjects was attributed to potent innate rather than adaptive responses.[109]

Vaccines to *Candida Albicans*

Much attention is now being given to the development of vaccines to establish long-lived immunological memory against *C. albicans* such that a robust and targeted adaptive immune response can be rapidly invoked upon secondary fungal challenge. The proteins selected for inclusion into anti *C. albicans* vaccines are predominantly (but not exclusively) those factors considered to be a requirement for virulence. One such class of molecules are the agglutinin-like sequence (Als) adhesins, which are required for the attachment of *C. albicans* to host surfaces during infection.[110,111]

By far the most well studied candidate for an anti *C. albicans* vaccine is Als3p (amino acids 17–432, referred to as NDV-3). Subcutaneous injection of NDV-3 in the presence of an adjuvant stimulated adaptive Th1/Th17 immune protection against *C. albicans* bloodstream infection in mice, resulting in the recruitment of activated phagocytes which facilitated fungal clearance from infected tissues.[112] Consistent with the differences in immune responses at different mucosal surfaces, vaccination of mice with NDV-3 results in the production of anti-Als3p IgG and IgA antibodies and reduced fungal burdens in vaginal tissues in a manner dependent upon both T- and B-lymphocytes, rather than the purely cell-mediated protection seen in bloodstream infections.[113] NDV-3 was also reported as being highly efficacious in a mouse model of OPC ,[114] has proven itself to be safe and immunogenic in human subjects, and is now being assessed in clinical trials.[115]

Mice vaccinated with an N-terminal region of Als1p are protected against a lethal innoculum of *C. albicans,*[116] with vaccination resulting in reduced fungal burdens in tissue following infection with *C. albicans*[117] and other *Candida* species.[118] Importantly, protection afforded by this vaccine is mediated via cellular rather than humoral means, as vaccination is still successful in B-cell deficient mice.[116] An MHC II-bound peptide fragment corresponding to a conserved region of ALS family proteins has been isolated from DCs infected with *C. albicans.*[119] The isolated peptide has been reported to act as a Th17 epitope and was observed to protect mice from fatal systemic candidiasis.[119]

Other families of *C. albicans* virulence factors have also shown promise as potential vaccine candidates, including the secreted aspartyl proteinases (Saps).[120] Immunisation of mice with Sap2p confers protective immunity in the face of an otherwise lethal systemic challenge of *C. albicans.*[121] Rats receiving intravaginal immunisation with amino acids 77–400 of Sap2p were protected against subsequent vaginal challenge with *C. albicans* in a manner dependent upon the generation of anti-Sap2p IgG and IgA.[122] As well as virulence factor vaccines, other formulations have been designed based on structural motifs. A vaccine containing the algal β-glucan laminarin has been reported to improve immune protection against[123] both vaginal (mucosal) and systemic *C.*

albicans infection in mice.[123] Despite this progress, success remains limited. No vaccines to *C. albicans* are clinically available at the time of writing. However, given the prevalence of fungal infections, particularly in the face of increasing resistance to commonly used anti-fungal therapies, the field of *C. albicans* vaccine design will no doubt continue to flourish and remain an area of intense study.

Concluding Remarks

Adaptive immune responses to *C. albicans* are crucial to the successful eradication of infecting fungus. Despite tremendous advances in our understanding of the molecular events that underpin adaptive immunity to this opportunistic fungal pathogen, there is still much to be discovered. It is worth noting here that much of our understanding of the adaptive immune responses to *C. albicans* is based on *in vitro* studies. However, these studies have so far correlated with *in vivo* findings and have provided us with a map of events in adaptive immune responses to this medically important fungal pathogen. Critically, as our understanding of the complex relationship between innate and adaptive immunity to *C. albicans* continues to evolve, and *in vivo* data are continually refined, future developments will no doubt enable the provision of improved medical outcomes for those who suffer from *C. albicans* infections.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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