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Cellular and molecular mechanisms of resistance to oral *Candida albicans* infections

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1. ABSTRACT

Oral candidiasis is a significant health problem in terms of both morbidity and economic outlay. Infections are predominantly caused by the commensal *C. albicans*, and affect immunocompromised individuals, including HIV-positive and AIDS patients, organ transplant recipients and chemotherapy patients. The molecular and cellular immune mechanisms involved in protection from and responses to oral candidiasis are overlapping, but distinct from those associated with other manifestations of the disease, including systemic, vaginal and gastric candidiasis. In oral candidiasis, clinical observations and experimental mouse models suggest a critical role for cell-mediated immunity. In mice, $CD4^+$ T-cells and the p40 subunit of interleukins 12 and 23 are strict prerequisites for resistance; however abrogation of IFN-gamma does not confer susceptibility. Here, we discuss this apparent inconsistency, and review the experimental evidence that clarifies which immune pathways are specifically involved in resistance and responses to candidiasis of the oral cavity. We also highlight deficiencies in the literature, particularly concerning the putative roles of some relatively new elements in immunobiology: interleukin-23, interleukin-17 and T helper (Th)17 cells.

2. *CANDIDA ALBICANS* AND CANDIDIASIS

Candida is one of the most frequently isolated fungal pathogens in humans. It can live as a harmless commensal in many different areas of the body and is carried by at least half the human population (1). In response to a change in environment, *Candida* can transform from a benign commensal into a disease-causing pathogen. There are approximately one hundred and fifty species of *Candida*, although only a small number of these are human pathogens (2). The *Candida* genus is composed of a heterogeneous group of organisms that grow as round or ovoid yeast cells (blastoconidia). Most members of the genus also produce filamentous pseudo-hyphae, and two species, including *C. albicans*, can also form true hyphae (2, 3). The ability to undergo reversible morphogenic transformation between yeast, pseudo-hyphae and true hyphae (phenotypic switching) contributes to the pathogenicity of *C. albicans*, at least partly because the hyphal form skews the host immune response to generate a favourable cytokine milieu for the yeast (4). This dimorphism is not only relevant to pathogenicity, but also to the clinical problems of diagnosis and treatment. Other attributes shown to be important in the pathogenicity of *C. albicans* include its abilities to adhere to host cells via

adhesins on the cell surface, and secrete proteinases and phospholipases (1).

Diseases associated with *C. albicans* infection occur in two discrete forms: systemic candidiasis (also known as invasive or disseminated), and mucosal candidiasis, which most commonly affects the oropharyngeal (oral), oesophageal and vaginal mucosal barriers. A combination of yeast virulence, environmental and host defence factors determine the various manifestations of the infection, and disease progression (3). Conversion from commensal to pathogen is mostly precipitated by alterations in the integrity of the host immune system, as well as treatment with antibiotics, intensive chemotherapy and immunosuppressive drugs (5). These infections present significant global health and economical problems, particularly amongst individuals with HIV infections and AIDS. The disease is associated with high morbidity, and mucosal colonisation is associated with systemic disease (6), where the mortality rate may be as high as 60% (7). Oral candidiasis incidence in HIV-positive children and adolescents was estimated to be around 27.5% in the year 2000 in the United States (8). This, along with the incidence of other opportunistic infections, has decreased significantly since the introduction of highly active anti-retroviral therapies (HAART) (8); however incidence rates amongst HIV-positive individuals are as high as 70% in developing countries (9-11), where HAART is not readily available.

3. HOST IMMUNE DEFENCE PATHWAYS IN HUMAN ORAL CANDIDIASIS: CLINICAL OBSERVATIONS

Studies of humans infected with *C. albicans* indicate that resistance to mucosal candidiasis is mediated by immune response pathways that are distinct from those that mediate resistance to systemic candidiasis (12). Individuals with congenital or acquired defects in cell mediated immunity are particularly susceptible to mucocutaneous, but not disseminated candidiasis (13). Systemic candidiasis is more commonly associated with myeloperoxidase deficiencies and neutropenia in debilitated or immunocompromised individuals in the hospital environment (12-16). The remainder of this review will focus on oral candidiasis; the reader is referred to other excellent reviews for a discussion of the host immune pathways important in systemic disease (7, 17).

Clinical and epidemiological data from humans suggest that cell-mediated immunity (CMI) is necessary for host defence against *Candida* in mucosal tissues (15). For example, oral candidiasis is most frequently found in individuals with CMI defects, including HIV-positive and AIDS patients (12), DiGeorge syndrome (thymic hypoplasia) (18), patients undergoing radiation and chemotherapy (3, 15) and organ/tissue transplant recipients (15). Furthermore, reduced CMI function in the peripheral circulation has been shown to lead to increased incidence of chronic mucocutaneous candidiasis (CMC) (19, 20). Individuals with CMC are selectively unable to clear *C. albicans* from mucosal surfaces, which results in persistent, debilitating infections affecting the skin, nails, and mucous membranes (21). CMC patients have impaired *Candida*-specific T-cell responses, defective lymphocyte proliferation and delayed type hypersensitivity responses to *C. albicans*, and there is a strong correlation between oral candidiasis incidence and reduced circulating $CD4^+$ T-cells (15, 21). CMC patients show impaired production of Th1 and Th1-regulatory cytokines (including IFN-gamma, IL-12 and IL-2), suggesting that there is a failure to mount a protective Th1 response against *C. albicans* (21). Importantly, these factors linked to oral candidiasis susceptibility in humans are strongly reproducible in animal models of the disease (see below).

4. BOTH INNATE AND ADAPTIVE IMMUNITY ARE INVOLVED IN RESISTANCE TO ORAL CANDIDIASIS

4.1. Phagocytes and pathogen-associated molecular pattern (PAMP)-receptors in oral candidiasis

The oral mucosa is a major entry portal for microbial flora, and is populated by multiple different professional phagocytes and innate effector cells (neutrophils, macrophages, monocytes, natural killer (NK) cells, dendritic cells (DCs), gamma/delta T-cells and other resident T-cells), which are capable of responding to the presence of "non-self", generating immediate effector responses and influencing host response pathways. Oral epithelial cells (OECs) also play an important role in innate defence, both producing and responding to pro-inflammatory cytokines (reviewed in (22)), and enhancing the effector functions of neutrophils (23). OECs can have direct candidastatic effects, which are more optimal with hyphae than conidia, and dependent on direct contact between fungal carbohydrate moieties and OECs (24). Additionally, OECs synthesise anti-candidal peptides, including beta-defensins, which help control fungal colonisation by direct anti-fungal action (involving cell wall thinning and reduced metabolism) and inhibiting fungal adherence to OECs (25).

As for the role of DCs in *C. albicans* detection and immune responsiveness in the oral mucosa, there is a considerable amount of *in vitro* evidence suggesting they are likely to be involved in detection and ensuing cytokine production. For example, DCs can phagocytose *C. albicans* conidia and hyphae, and subsequently become activated, producing functionally distinct DC subsets with differentially-polarised cytokine secretion profiles depending on the pathogen-associated molecular pattern (PAMP)-receptors utilised for phagocytosis (26-28). This is further supported by the fact that Langerhans cells (epithelial DCs) are present in the oral mucosa (29) with higher numbers in candidal lesions (30, 31); however to our knowledge the function of DCs in oral candidiasis has not been unequivocally demonstrated in an *in vivo* system.

In the case of *C. albicans*, there is clear experimental evidence showing that toll-like receptors (TLR)-2, TLR-4, TLR-9, Fc-gamma-R, dectin-1, DC-SIGN, complement receptor 3 (CR3), and the mannose receptor can mediate recognition of *C. albicans* and/or its

fungal wall components (including glucans, mannans and mannoproteins) (28), although it is not known which of these actually function in oral mucosal defence against *C. albicans*. Recent work has focussed on delineating the downstream signalling pathways by which these receptors collaborate and cross-regulate each other to ultimately generate a Th1-polarised cytokine profile (27, 32-34). Work from Kullberg's laboratory demonstrated that morphogenic transformation of *C. albicans* to the pathogenic hyphal state is associated with loss of protective TLR-4-mediated proinflammatory cytokine production and increased TLR-2 signalling in macrophages, leading to exaggerated production of anti-inflammatory IL-10 (4) and enhanced survival of TGF-beta-producing regulatory T (Treg)-cells (35). The relative expression of PAMP-receptors involved in *C. albicans* recognition by leukocytes in the oral mucosa has not been properly established, nor have PAMP-receptor gene knockouts been studied in the context of oral candidiasis susceptibility. Further characterisation of these *Candida*-host cell interactions in the oral mucosa should be a research priority as they may represent specific drug targets, and are accessible to topical agents for treatment of oral candidiasis. (For a more detailed discussion of Candida-host receptor interactions, refer to (32)).

Soluble candidastatic and candidacidal proteins such as mucins, histatins, defensins and calprotectin, are produced by OECs and serous cells of the salivary glands and also help minimise fungal colonisation. The experimental evidence supporting roles for secreted factors (including salivary proteins and antibodies) in protection against oral candidiasis will not be discussed here; the reader is instead referred to comprehensive reviews for further discussion (36, 37).

4.2. Leukocyte function in oral candidiasis: insight from experimental mouse models

Oral *C. albicans* infection models have become valuable tools for investigating the cellular and molecular pathways involved in innate and adaptive oral *C. albicans* defence *in vivo* (38, 39). Much of what we know about the response to oral *C. albicans* challenge is derived from monitoring the oral fungal burden, cytokine expression patterns, lymphocyte and phagocyte function in cytokine knockout mice (see below), and also comparing these parameters between resistant and susceptible mouse strains. The course of oral *C. albicans* infection in wild-type, immunocompetent mice was first established in the CD1 strain (40). Upon initial exposure, there was an inflammatory response that resolved in less than 8 days, and correlated with clearance of yeast from the oral mucosa. This course of infection was consistent with other "resistant" strains tested (BALB/c and C57BL/6J; (41), whereas "susceptible" strains were found to have heavier fungal colonisation (CBA/CaH; (42)) and/or prolonged fungal clearance rate (up to 15 days in DBA/2 mice; (43, 44). At the most basic level, these strain-dependent differences provide evidence that genetic background affects susceptibility to oral candidiasis, and also provide benchmark data demonstrating the normal course of infection in experimental mice.

4.2.1. $CD4^+$ and $CD8^+$ T-cells

Oral *C. albicans* infection models using immunodeficient "nude" mice have been established to study the role of cell-mediated immunity in oral candidiasis (45, 46). Nude mice lack functional T-cells, analogous to DiGeorge syndrome in humans. Our previous studies showed that upon oral challenge with *C. albicans*, these mice demonstrated significantly increased oral colonisation compared to heterozygous littermates, resulting in a severe, chronic infection that persisted for more than three months, supporting the idea that T-cells are essential for oral *C. albicans* resistance. Thymus transplant, or adoptive transfer of $CD4^+$, but not $CD8^+$ T-lymphocytes, significantly reduced the fungal burden in oral tissues, eventually leading to recovery (45). Following reconstitution, lymphocytes from the submandibular and superficial cervical lymph nodes produced IFN-gamma, and large amounts IL-12. In a separate study profiling cytokine production in the oral mucosa four days after *C. albicans* infection we showed that lymphocyte reconstitution stimulated production of TNF-alpha, suggesting that $CD4^+$ T-lymphocytes mediate a protective, Th1-polarised response to oral *C. albicans* challenge (47) (refer to Figure 1).

Interestingly, although these studies demonstrate that physical and/or functional $CD4^+$ T-cell deficiency is necessary to generate oral candidiasis, it was not sufficient in antibody-meditated $CD4^+$ T-cell depletion experiments (48). Head and neck irradiation, a known inducer of oral mucosal inflammation and tissue damage, and risk factor for oral candidiasis (49, 50), was required in addition to $CD4^+$ T-cell depletion to generate higher fungal burdens and prolong disease. This could reflect that local mucosal defences are also involved in oral candidiasis resistance, that antibody-mediated depletion of $CD4^+$ T-cells is not as efficient as genetic depletion, or that the two different means of generating the deficiency have uncharacterised, differential effects. Again, cytokine expression analysis indicated that the heavier fungal burden in the $CD4^+$ T-cell-depleted, irradiated mice was associated with impaired IFN-gamma production in draining lymph nodes (51), consistent with previous conclusions that Th1 responses are necessary for resistance to oral candidiasis. Thus the majority of conclusive evidence suggests an important requirement for $CD4^+$ T-cells in resistance to oral candidiasis.

$CD8^+$ T-cells also appear to be involved in defence against oral *C. albicans* infection, but evidence suggests they are not as indispensable as $CD4^+$ T effectors, and may in fact be a second line of defence against oral candidiasis in the absence of functional $CD4^+$ T-cells (reviewed in (52)). They are present at infection sites in both mice and humans (31, 43, 53, 54), can directly inhibit the growth of *C. albicans* hyphae *in vitro* (55), can secrete macrophage and neutrophil-activating cytokines, and therefore may contribute to the inflammation at Candida infection sites. However they cannot correct the susceptibility of nude mice to oral candidiasis (45). Furthermore, their migration to the outer epithelium in infected humans is incomplete, with accumulation at the

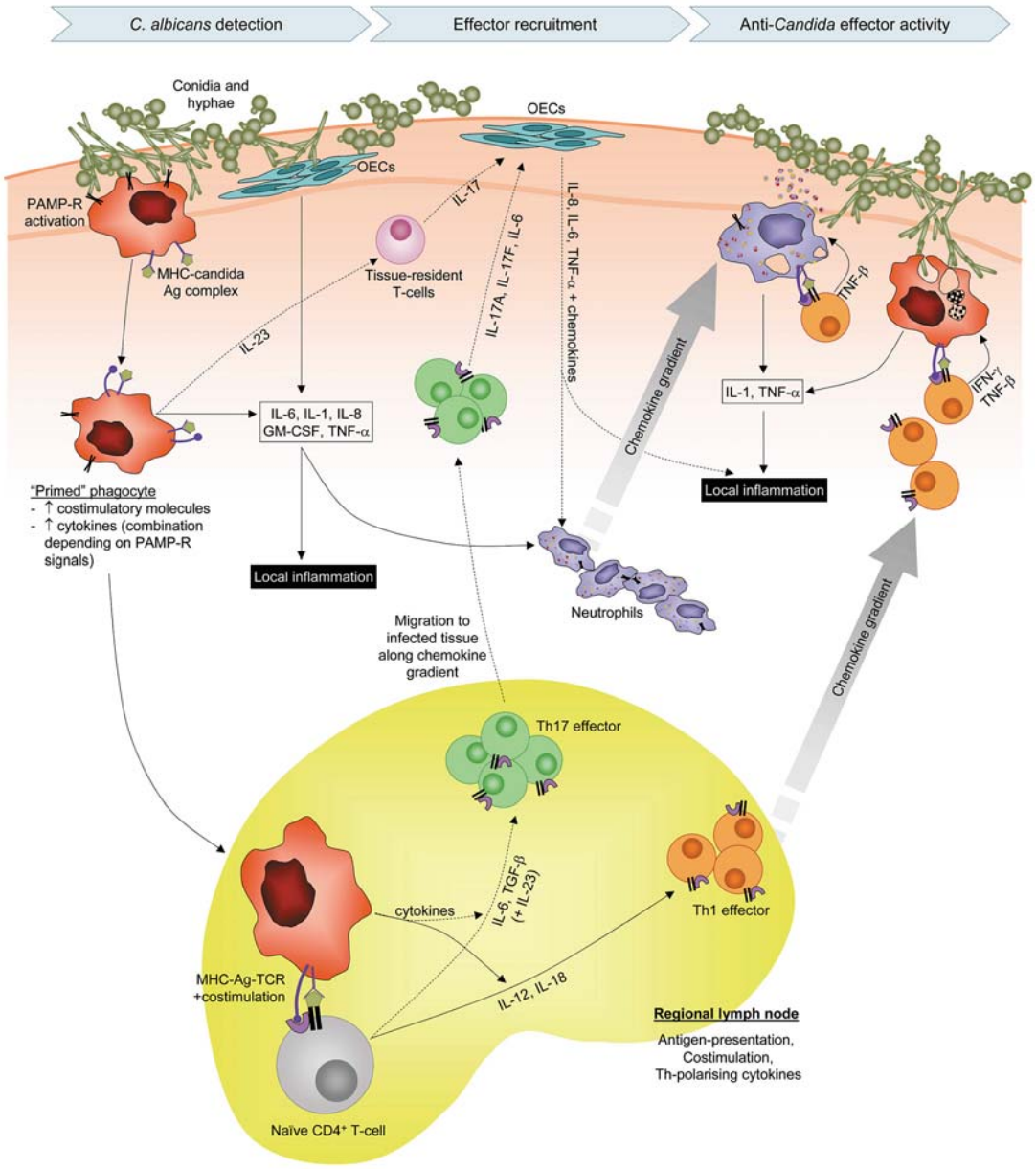

Figure 1. Experimentally-confirmed and putative host response pathways involved in oral candidiasis. Antigen presenting cells (APCs) at the host-pathogen interface phagocytose *C. albicans* conidia and hyphae, present antigens (Ag) on MHC, and become "primed" for activation. Priming is initiated by activation of pathogen-associated molecular pattern receptors (PAMP-R), which subsequently induces (↑) costimulatory molecules (e.g. CD40) and cytokines (e.g. IL-12 or IL-23). Oral epithelial cells (OECs) also detect invading *C. albicans* and respond by secreting cytokines that attract neutrophils to the site, and contribute to the general pro-inflammatory milieu. Some primed APCs migrate to lymph nodes where they present *Candida* Ag to naïve CD4+ T-cells (Th0). Secretion of IL-12 and IL-18 by APCs promotes differentiation and clonal expansion of antigen-specific Th1 effector clones, which migrate to affected tissues along a chemokine gradient established by epithelia and phagocytes at the site of infection. Th1 cells secrete IFN-gamma and TNF-beta, which act in a paracrine fashion on APCs displaying complementary MHC-Ag complexes, activating their effector functions (phagocytosis, phagolysosome formation, respiratory burst, degranulation and enhanced Ag-presentation), resulting in yeast clearance. It is also possible that Th17 clones form in regional lymph nodes, dependent on production of IL-6, TGF-beta and IL-23 by APCs. Th17 cells may then contribute to local inflammation and neutrophil infiltration by producing IL-17 and additional IL-6. There may also be an alternative innate IL-17 pathway in which tissue-resident T-cells (e.g. gamma/delta) are activated by IL-23 from primed phagocytes to produce IL-17. IL-17 induces production of pro-inflammatory cytokines and neutrophil chemoattractants from epithelial and stromal cells at the infection site. *Solid lines indicate experimentally-validated pathways; dotted lines indicate putative pathways*

lamina propria border, suggesting that their role in anti-candidal defence may be limited (52, 53), possibly due to down-regulation of E-cadherin in infected epithelium (56).

4.2.2. Gamma/delta T-cells

Chakir and colleagues (1994) reported that BALB/c and DBA/2 mice, which share the same major histocompatibility complex (MHC) haplotype ($H\text{-}2^d$), showed different kinetics of primary oral *C. albicans* infection after topical application of the same inoculum. Both strains recruited $CD4^+$ and $CD8^+$ T-cells during the infection, however there was time-specific recruitment of gamma/delta T-cells coincident with a dramatic decrease in viable *Candida* in mucosal tissue (43). Using identical mouse strains, Elahi *et al* (2000) demonstrated that there was selective expansion of gamma/delta T-cells in regional lymph nodes that correlated with *C. albicans* clearance. While the prevalence of gamma/delta T-cells in infected *C. albicans* mucosa is predictable, little is known about the functions of these cells in general, l*et al*one their possible function in resistance to oral candidiasis. Gamma/delta T-cells are enriched in epithelia, and are thought to regulate both inflammation and ensuing adaptive responses (57). T-cell receptor delta-chain knockout mice ($TCR\text{-}delta^{-/-}$; deficient in gamma/delta T-cells) have been used to study host response pathways in vaginal candidiasis, and interestingly were found to be more resistant to vaginal infections than wild-type mice, implying they serve a regulatory role (58), however these mice have not been studied in oral infection models. It has been suggested that gamma/delta T-cells may provide an alternative pathway to macrophage activation during the immune response to *C. albicans* (59).

4.2.3. Candidacidal effector cells

The effector cells involved in the elimination of invading *C. albicans* hyphae in the oral mucosa are primarily monocytes, macrophages and neutrophils, with neutrophils being especially critical for preventing invasive infection (15). Upon binding to fungal wall components, PAMP-receptor signalling results in enhanced phagocytosis and antigen presentation, respiratory burst (dramatically enhanced production of reactive oxygen intermediates), enhanced synthesis of lysosomal cathepsins and hydrolytic enzymes and degranulation (reviewed in (33, 60)). Functional depletion of neutrophils and monocytes significantly increased the oral fungal burden in mouse models (48). Furthermore, *C. albicans* stimulated chemoattraction of neutrophils in a reconstituted human oral epithelium, which was associated with enhancement of Th1 cytokine (IL-12 and IFN-gamma) production, and protection from *Candida*-induced tissue damage (61). Macrophage and neutrophil phagocytosis of *C. albicans* yeasts has also been reproducibly captured *in vitro*, with evidence that this can occur in three-dimensional space mimicking the infected oral mucosa (62). The phagocytic and candidacidal functions of phagocytes are potently activated by IFN-gamma, which is predominantly derived from activated Th1 effector cells, and is thought to act in a paracrine fashion on phagocytes presenting appropriate *Candida* antigens and expressing CD40 (33) (see Figure 1).

4.3. Cytokines in host defence against oral candidiasis

There is substantial experimental evidence demonstrating that professional phagocytes (and possibly DCs) are critical for maintaining the integrity of the oral mucosal barrier, and that they can also instruct adaptive T-cell responses against *C. albicans* by helping to establish a cytokine milieu that favours the proliferation and differentiation of IFN-gamma-producing Th1 effector cells (see Figure 1). Clearance of oral *C. albicans* infections also involves OECs, $CD4^+$ T-cells and gamma/delta T-cells. Calculated activation and cross-communication between these cell types, and also appropriate resolution of Th1 and inflammatory responses, are mediated by complex cytokine networks. The local inflammatory and Th1 signature cytokines produced during oral *C. albicans* infections are reasonably well-characterised, however several questions remain regarding the potential roles of several relatively new players in cytokine biology.

4.3.1. Cytokines in the oral mucosa: acute phase inflammation and instruction of adaptive responses

Acute oral *C. albicans* infections are generally followed by a typical acute-phase response in the oral mucosa. After incubation with *C. albicans*, primary human oral epithelial cells produce IL-6 (an important pyrogenic, pro-inflammatory and Th17-inducing cytokine), granulocyte macrophage colony-stimulating factor (GM-CSF; which stimulates proliferation of granulocytes and monocytes in myeloid tissue), and also IL-8 (a potent neutrophil chemoattractant) (63, 64). Separate studies utilising a reconstituted human oral epithelium concurred that infection with *C. albicans* induced strong expression of GM-CSF, IL-8 and TNF-alpha, and moderate stimulation of IL-1alpha, IL-1beta, IL-1RA, IL-6 and IFN-gamma (61, 65, 66). It is noteworthy that cytokine production coincided with infiltration of supplemented neutrophils (61), supporting the idea that the acute-phase response instigated by OECs is responsible for initiating leukocyte infiltration. There have been no quantitative expression studies documenting the kinetics of cytokine production in human oral epithelium, however it is clear that there is generalised induction of proinflammatory cytokines, and that these are at least partly derived from OECs themselves.

In experimental oral candidiasis, IL-6, TNF-alpha and IFN-gamma have been detected in the oral mucosa of both naïve and infected mice (48). The degree of induction following *C. albicans* infection is not known because this analysis was not quantitative, although abrogation of the TNF-alpha gene in C57BL/6J mice significantly increased the severity, but not the duration, of oral *C. albicans* infection (41), suggesting that TNF-alpha is important in mucosal defence. Furthermore, oral administration of recombinant TNF-alpha significantly reduced oral yeast carriage in experimental mouse models (67), and conversely, anti-TNF-alpha antibody therapy can cause oral candidiasis in humans (68), further supporting the contention that this cytokine is important in resistance to oral candidiasis. Interestingly, in nude mice, TNF-alpha was only detected in the infected oral mucosa after lymphocyte reconstitution (47), suggesting T-cells are required for its production.

4.3.2. Lymphocyte and antigen-presenting cell-derived cytokines in mice with oral candidiasis: adaptive responses

C. albicans-derived mannoprotein can induce expression of IFN-gamma, IL-1beta, TNF-alpha, GM-CSF, IL-6 and IL-2 mRNA from human primary peripheral blood mononuclear cells, but no or very low levels of IL-4, IL-10, and TGF-beta2 (69), consistent with the well-accepted view that *C. albicans* antigens principally induce Th1 responses. We have shown that inoculation of wild-type BALB/c mice with *C. albicans* significantly induces IL-12 and IFN-gamma in regional lymph nodes (submandibular and superficial cervical) of BALB/c mice between days 1 and 4 post-infection (48). Furthermore, adoptive transfer of lymphocytes from wild-type mice into *nu/nu* (nude; T-cell-deficient) counterparts results in recovery from severe, chronic oral candidiasis, and is also associated with a surge in IL-12 and IFN-gamma production in regional lymph nodes (45). Collectively, our studies suggest an important role for the IL-12-IFN-gamma axis in clearance of *C. albicans* from the oral mucosa.

As expected, mice made deficient in IL-12 by abrogation of the gene encoding its p40 subunit develop oral candidiasis that is more severe and chronic than in T-cell-deficient nude mice (13, 41). However, the oral fungal burden in IFN-gamma knockout mice is no different to wild-type animals, and the very mild infection resolves in the same time-frame, indicating IFN-gamma abrogation does not increase susceptibility to oral candidiasis (41). Interestingly, humans with deficiencies in the IFN-gamma receptor are not susceptible to candidiasis either, although they are susceptible to infections with mycobacterial and salmonella infections (70). One possible interpretation of the mouse models is that IFN-gamma may not play a key role in mucosal defence in immunocompetent mice, and that there may be no requirement for an adaptive response involving IFN-gamma if the mucosal barrier is intact. In addition, the two knockouts ($p40^{-/-}$ and IFN-$gamma^{-/-}$) are not directly comparable because the p40 subunit is shared with a relatively new member of the heterodimeric cytokine family – IL-23 (71) – and therefore the IL-12-IFN-gamma axis is not the only affected pathway in these mice. Concomitant abrogation of IL-12 and IL-23 may have implications for both innate mucosal defence and adaptive responses, and could explain the severe phenotype of IL-12/23$p40^{-/-}$ mice (see below for further discussion). Interestingly, humans deficient in either of the IL-12 receptor subunits do not have an increased incidence of candidiasis (70). The function of IL-23 in oral mucosal defence against *C. albicans* has not been investigated. The p40 subunit is also known to form homodimers, which could contribute to the phenotype of the p40 knockout. Specific immunobiological functions of p40 homodimers have not been described, however they are produced in physiologically-relevant amounts, and can antagonise the IL-12 receptor in mice but do not appear to have this effect in humans (72).

Whilst there is an unmistakable requirement for Th1 responses in defence against oral candidiasis, a survey of the literature may give the impression that Th2 effector cells also play a role. This is mainly due to difficulty in interpreting the apparent induction of IL-4 in regional lymph nodes of immunocompetent mice during experimental oral *C. albicans* infection (44, 48). Moreover, Elahi and colleagues demonstrated that antibody-mediated inactivation of IL-4 results in elevated oral yeast carriage and delayed clearance (44), and DCs are known to produce both IL-12 and IL-4 in response to phagocytosed *C. albicans* (28). These results have been a paradox in the field because IL-4 is historically linked to Th2 responses, which are associated with susceptibility to oral candidiasis, not resistance (73). Adding to this uncertainty are conflicting results from our laboratory showing that abrogation of the IL-4 gene in the same strain as the aforementioned studies (BALB/c), has no effect on oral fungal burden (41). Given the lack of any heightened disease susceptibility in IL-$4^{-/-}$ mice, and that the degree of IL-4 induction by *C. albicans* is many orders of magnitude lower than overt Th2-inducing agents like respiratory allergens (74, 75), yet IL-4 can be detected in response to *C. albicans in vitro* and *in vivo*, it may be possible that IL-4 serves an immuno-regulatory role in oral candidiasis even though it may not be essential for resistance to infection. It is worth noting that although Th2 polarisation is the most well-understood and historical function of IL-4, it can also induce secretion of IL-12 from human monocytes (76), supporting the more progressive view that assigning cytokine functions in particular disease states based on their classification within the Th1/Th2 dichotomy may be overly simplistic (77).

4.3.3. Role of IL-12/23p40 in resistance to oral candidiasis

The heterodimeric structure of the IL-12 family, which includes IL-23 and IL-27, is unique amongst cytokines (78). IL-12 is comprised of disulphide-linked subunits: p35 is homologous to the four-helix bundle (type I) cytokine superfamily, and p40 is homologous to the extracellular domains of the type I cytokine receptors (79, 80). p35 is expressed in many cell types, but is secreted only when partnered with p40, thus both must be expressed in the same cell to generate the biologically-active heterodimer (IL-12p70). p40 expression is highly induced by PAMP-receptor signalling, and restricted to professional phagocytes and epithelial cells (79, 81). The IL-12 receptor (IL-12R) is also heterodimeric, with the beta1 subunit interacting primarily with p40, and beta2 subunit (the signal-transducing component) interacting mostly with p35 (81). IL-12R is expressed mainly on resting and activated T and NK cells, and signals through Jaks, Stat4 and NF-kappaB, resulting in commitment to the Th1 lineage and induction of the IL-18 receptor in differentiating Th1-cells, and profound induction of IFN-gamma in both Th1 and NK cells. IL-12 initially acts alone, but then synergises with IL-18 to stabilise the Th1 phenotype (82). IL-12/23$p40^{-/-}$ mice develop normally and are

fertile, but are severely lacking in IFN-gamma inducibility and Th1 immune responses (83), exemplifying the critical role for IL-12 as a Th1 immunopotentiating cytokine.

As previously mentioned, the p40 subunit is shared with IL-23 (71). The second subunit of heterodimeric IL-23 is p19, which like p35, is a type I cytokine. Expression of active IL-23 is also restricted to professional phagocytes. The mechanisms regulating expression of p35 and p19 have not been fully characterised, but it has been suggested that there may be distinct subsets of phagocytes expressing either IL-12 or -23 (79). The IL-23 receptor shares the beta1 subunit with IL-12R, but comprises a second, unique IL-23R component that binds predominantly to p19 (84). IL-23 functions appear to be centred on generating localised inflammation. This is achieved by promoting the production of IL-17, which in turn acts on monocytes and epithelial, endothelial and stromal cells, inducing the production of multiple chemokines and proinflammatory cytokines, the defining effects of which are inflammation, neutrophilic infiltration and thus heightened immune surveillance and cytotoxic activity in infected tissues (reviewed in (82) (see Figure 1).

In adaptive immunity, IL-23 contributes to the differentiation of Th17 effector cells, specialised in IL-17 production, from naïve or memory CD4+ T-cells. In humans, Th17 differentiation is driven by IL-23 along with IL-1beta, and possibly IL-6, and is inhibited by TGF-beta (85, 86). In mice, IL-23 cannot induce differentiation (this is driven by IL-6, TGF-beta and IL-1 (87-89), but acts on partially-differentiated cells to generate full commitment to the Th17 phenotype, analogous to the role of IL-18 in Th1 differentiation (87, 90). Uhlig and colleagues recently showed that mucosal pathology in an experimental mouse model of colitis was dependent on IL-23 produced in the gastrointestinal mucosa, and completely independent of both T-cells and IL-12 (91). In light of these results, and also that IL-23 is produced locally by phagocytes in mice within a few hours of activation, inducing secretion of IL-17 (and also TNF-alpha and IL-1beta) from tissue-resident T-cells (79), Kastelein *et al* have proposed that in addition to its role in Th17 differentiation, IL-23 may have an important role in the innate immune system in generating immediate inflammation and neutrophil recruitment.

There are several precedents supporting the hypothesis that the IL-23-IL-17 axis may be involved in protection against oral candidiasis. Firstly, an adjunct to the aforementioned findings that IL-12/23p40$^{-/-}$ mice, but not IFN-gamma$^{-/-}$ mice (41), IFN-gamma receptor or IL-12 receptor-deficient humans (70), develop severe oral candidiasis, are unpublished observations from our laboratory showing that intraperitoneal injection of recombinant murine IL-12 does not correct the phenotype of IL-12/23p40$^{-/-}$ mice. This treatment does generate transient reductions in oral yeast carriage, however after one week there is no difference between treated and untreated mice, with several different injection schedules trialled *(manuscript in preparation)*. Collectively, these findings could just highlight differences in host immune response pathways to *C. albicans* in humans and mice, but could also reflect a requirement for IL-23. Secondly, others have shown that the IL-23-IL-17 axis is involved in host responses to other fungi: *Pneumocystis carnii* in the bronchial mucosa (92), and systemic infections with both *Cryptococcus neoformans* (93) and *C. albicans* (94). Third, administration of purified beta-glucan (a *C. albicans* fungal wall component) to mice resulted in the production of both IFN-gamma and IL-17 in lymph nodes (95). Finally, DCs incubated with *C. albicans* antigens (95) or live yeast (96), can instruct differentiation of Th17 cells *in vitro*. The balance of Th1 and Th17 responses generated by *C. albicans* may depend on the proportion of yeast (which promote Th1) versus hyphae (Th17) to which antigen presenting cells are exposed (96). Addition of excess IL-12 has been shown to skew differentiation towards Th1, whereas IL-23 preferentially instructed Th17 differentiation (96), suggesting that *in vivo* there could be a critical balance of Th1 and Th17 effectors in response to *C. albicans* infection.

Interestingly, a recent report by Zelante *et al* showed that IL-23p19-/- mice are actually protected against gastrointestinal candidiasis in experimental mice despite increased candidacidal activity of p19-/- neutrophils *in vitro*, probably by suppressing protective Th1 responses, and promoting prolonged local inflammation that opposes appropriate resolution of the response, leading to pathology (97). The authors found similar results with systemically-infected p19-/- mice, which contrasts with an earlier report showing that an IL-17 response is required for resistance to systemic candidiasis, using IL-17 receptor knockout mice (94). Clearly there is much to be resolved in this field, particularly in dissecting apart the cross-regulatory from effector functions of Th1 and Th17 cytokines. Additionally, it is likely that there will be differences in the involvements of these two pathways depending on the infection site, thus a clear research priority is to characterise these pathways in an oral candidiasis model.

5. ANALYSIS OF *C. ALBICANS*-INDUCED GENE EXPRESSION AND CYTOKINE SIGNALLING NETWORKS IN IL-12/23P40$^{-/-}$ MICE

As described above, we have previously demonstrated that IL-12/23p40 is a critical mediator of resistance to oral candidiasis (41). This finding prompted us to investigate the host response pathways activated by oral *C. albicans* infection in these mice at the molecular level, with the intention of further characterising the alterations associated with p40 deficiency. We conducted comparative gene expression analysis on whole lymph

nodes (superficial cervical and submandibular) and oral tissues (tongue, palate and buccal mucosa) from $p40^{-/-}$ knockout (KO) and C57BL/6J wild-type (WT) controls, in both naïve and *C. albicans* infected states, using pooled RNA from five mice for each treatment, and Affymetrix cDNA microarrays. The time-point chosen for analysis was day 6 post-infection, which corresponds to a time that is early enough to capture wild-type mice in the infected state (infections generally clear very rapidly in these mice), but late enough for any adaptive host responses to commence. This preliminary array data allows some generalisation about the pathways that might be important in oral *C. albicans* infection, and provides clues about the molecular differences between WT and p40 KO mice. To date we have validated expression of three genes from the list of genes with altered expression in KO mice upon infection: CD4 (-2.6 fold change in the lymph nodes by array analysis, -2.9 fold by real-time PCR), CD8 (-1.9 and -1.4 fold changes by microarray and real-time PCR respectively) and β-defensin 4 (-4.0 and -8.0 fold changes by microarray and real-time PCR respectively).

In infected WT mice, we found that expression of 45 and 24 genes was altered at day 6 post-infection in the oral tissues and lymph nodes respectively (≥ 2 fold change compared to the uninfected state). There was marked up-regulation of soluble inflammatory markers and proteins involved in tissue remodelling in the oral mucosa (see Table 1), which is consistent with the "healer" phenotype of the mice at day 6 post-infection (41). There was little gene regulatory activity in the lymph nodes, suggesting there was no major lymphocyte proliferation or differentiation occurring at this timepoint.

Conversely, oral *C. albicans* infection of p40 KO mice generated 72 and 104 gene expression alterations in oral tissues and lymph nodes respectively (≥2-fold compared to uninfected mice), which is considerably higher than the number in WT mice. One general observation regarding the infection-induced genes in p40 KO mice is that there are multiple examples of down-regulated genes that would actually be expected to increase in response to oral *C. albicans* invasion (Table 1). For example, in the oral tissues there was down-regulation of beta-defensin (Def-beta)-4. Defensins have been implicated in oral resistance to *C. albicans* (25, 98, 99), and Def-beta-1 and -3 were actually up-regulated by infection in the oral mucosa of WT mice (Table 1). Another curious finding was down-regulation of one of the small proline-rich proteins (1B), which are involved in epithelial cornification, and were markedly up-regulated in WT mice at this timepoint. In the lymph nodes, there was a decrease in the expression of multiple genes involved in T-cell development, differentiation and antigen presentation (e.g. Rag-1, Tap-like, Cd4, Cd8, Shc1, Tapasin, Tcrb-j, Pecam-1, IL-1F5, IL-1F6, IL-F8 and CD86/B7.2; see Table 1), which would be expected to increase in the face of immunological challenge, or perhaps remain unchanged in the context of an IL-12/23 deficiency. The reasons behind this phenomenon are not clear, although it is possible that in the absence of IL-12 and IL-23, immunosuppressive cytokines that normally maintain a critical balance with immunopotentiating cytokines to prevent pathological overactivity, may dominate to produce global repression of cell-mediated immune responsiveness. For example, *C. albicans*-induced signalling through TLR-2 promotes macrophage production of IL-10, and survival of TGF-beta-producing Treg cells (35). Both IL-10 and TGF-beta counterbalance the effects of IL-12 by suppressing the differentiation of Th1 cells, and also Th17 cells in the absence of IL-23 (100).

We propose that the large differences in the numbers of infection-induced gene regulatory events between WT and p40 KO mice, particularly in the lymph nodes (24 versus 104 respectively), may exist because there is simply no requirement for a major host response in WT mice, in which the mucosal barrier is intact. Conversely, in p40 KO mice both the mucosal barrier and the second line of defence are abrogated through deficiencies in both IL-23 and IL-12, allowing hyphae to penetrate the mucosa and activate adaptive defence pathways. Indeed, this hypothesis is consistent with the phenotype of the mice: severe infection that lasts in excess of three months, and easily-identifiable focal sites of fungal invasion with extensive hyphal penetration of the oral epithelium (41). This would also be consistent with the finding that mice genetically deficient in IFN-gamma, which is not directly involved in innate immune function, but is essential for effective Th1 responses, are actually resistant to oral candidiasis (41). In both mice and humans, *C. albicans* oral mucosa invasion is usually associated with the formation of neutrophilic microabscesses that also contain DCs, CR3+ phagocytes and T-cells (CD4+, CD8+ and gamma/delta) (13, 22). However in p40 KO mice, there are no obvious differences to WT mice in the presence of CD4+, CD8+, CD14+ (macrophages and neutrophils), CD1+ or CD83+ DCs ((41), and unpublished observations), suggesting there could be a leukocyte recruitment defect in the p40 knockout. Given that IL-23 has previously-demonstrated roles in IL-17-mediated leukocyte recruitment (see above and Figure 1); it is possible that abrogation of p40 affects not only the IL-12-Th1 axis, but also IL-17-mediated production of critical chemokines in the oral mucosa. This would certainly be consistent with our observation that IL-12 replacement does not correct the phenotype in these mice.

6. PERSPECTIVE

In conclusion, studies from our laboratory point to a significant involvement of p40 in resistance to oral candidiasis, but the exact involvement of IL-12 and/or IL-23 is yet to be determined. We are currently

Table 1. Selected genes with altered expression in oral tissues and lymph nodes of C57BL/6J (WT) and IL-12/23p40$^{-/-}$ (KO) mice 6 days after oral *C. albicans* infection

WT mice: oral tissues				
FC	**Gene Symbol**	**Gene Title**	**Known functions in immune response pathways**	**References**
-5.36	Dbp	D site albumin promoter binding prot		
-5.14	Smr1	submaxillary gland androgen regulated protein 1		
-5.12	Dbp	D site albumin promoter binding prot		
-3.56	Per3	period homolog 3 (Drosophila)		
74.54	S100a8	S100 calcium binding protein A8 (calgranulin A)	Calgranulin/calprotectin/A1 antigen: one of the S100 family of Ca-binding proteins. Secreted by neutrophils and implicated in acute and chronic inflammation. A marker of infiltrating macrophages. Associated with oral candidiasis in humans.	(84, 85)
55.81	S100a9	S100 calcium binding protein A9 (calgranulin B)		
19.16	Sprr2j	small proline-rich protein 2J	Small proline-rich proteins are involved in barrier function of stratified epithelia. Expressed in normal keratinocytes and respond differently to environmental insults. Involved in formation of the cornified cell envelope late in epithelial differentiation (cornification), which is essential to protect against environmental attack and water loss. Increased expression is associated with inflammatory conditions.	(86)
18.9	Saa1	serum amyloid A 1	One of the hepatic acute-phase inflammatory proteins, induced by cytokines (TNF-alpha, IL-6 and IL-1). May be induced up to 1000 fold in inflammatory states. Can induce MMPs, collagenase and other ECM-degrading proteins. May also play a role in leukocyte chemotaxis. In the blood aids in lipid transport and metabolism in inflammatory situations that result in liberation of lipid membranes from tissue destruction.	(87)
18.67	Sprr2d	small proline-rich protein 2D	See Sprr2j above	
15.83	Sprr2f	small proline-rich protein 2F	See Sprr2j above	
10.36	Defb3	defensin beta 3	beta-defensins are antimicrobial proteins secreted by oral epithelia with demonstrated direct anti-candidal effects.	(21, 81, 82)
8.77	Sprr2h	small proline-rich protein 2H	See Sprr2j above	
6.7	Npas2	neuronal PAS domain protein 2		
5.92	Chi3l1	chitinase 3-like 1		
5.52	Ear5	eosinophil-associated, RNAse A5		
4.22	Uox	urate oxidase		
4.03	Ube2c	ubiquitin-conjugating enzyme E2C		
3.08	Igh-VJ558	immunoglobulin heavy chain (J558)	Segment of the heavy chain immunoglobulin locus	
3.05	Sprr2a	small proline-rich protein 2A	See Sprr2j above	
2.58	Defb1	defensin beta 1	See Defb3 above.	
2.05	Sprr1b	small proline-rich protein 1B	See Sprr2j above	
WT mice: lymph nodes				
FC	**Gene Symbol**	**Gene Title**	**Functions in immune response pathways**	**References**
-6.35	Mup1	major urinary protein 1		
-4.72	Bpnt1	bisphosphate 3'-nucleotidase 1		
80.45	Spt1	salivary protein 1	Very abundant in saliva; function not known.	
18.28	Foxa1	forkhead box A1		
3.71	Ebf1	early B-cell factor 1	Transcription factor implicated in specifying the B-cell lineage commitment gene expression program.	
KO mice: oral tissues				
FC	**Gene Symbol**	**Gene Title**	**Functions in immune response pathways**	**References**
-5.7	Nmu	neuromedin		
-5.5	Krtap13	keratin associated protein 13		
-5	Klrc2	killer cell lectin-like receptor subfamily C, member 2		
-4.6	2310007F04Rik	RIKEN cDNA 2310007F04 gene		
-4	Defb4	defensin beta 4	See Defb3 above.	
-2.6	Il1f5	interleukin 1 family, member 5 (delta)	A member of the IL-1 superfamily of cytokines. Function not fully understood.	(88)
-2.5	Il1f6	interleukin 1 family, member 6	IL-1F6 is expressed predominantly in epithelia and is a member of the IL-1 superfamily of cytokines. It acts via IL-1Rrp2 (MAPK and NFkB pathways) to induce IL-6 and IL-8 in epithelial cells, therefore promotes inflammation and neutrophil recruitment.	(88)
-2.2	Il1f8	interleukin 1 family, member 8	IL-1F8 is expressed predominantly in epithelia and is a member of the IL-1 superfamily of cytokines. It acts via IL-1Rrp2 (MAPK and NFkB pathways) to induce IL-6 and IL-8 in epithelial cells, chondrocytes and synovial fibroblasts; promotes inflammation and neutrophil recruitment.	(88)
7.7	Crisp1	cysteine-rich secretory protein 1		

4	2200003E03Rik	RIKEN cDNA 2200003E03 gene		
KO mice: lymph nodes				
FC	**Gene Symbol**	**Gene Title**	**Functions in immune response pathways**	**References**
-48.8	Rag1	Recombination activating gene 1	Catalyses recombination between segments of T-cell receptor and immunoglobulin genes. Functional disruption by homologous recombination leads to immunodeficiency due to lymphoid arrest at a stage prior to the recombination of the antigen receptor loci. Rag-1 and -2 were once thought to be irreversibly downregulated by positive selection, but they can be re-expressed in peripheral lymphoid tissues dependent on a local inflammatory environment. Rag expression can be reactivated in CD4+ T-cells by chronic antigen exposure. RAG expression can also be reactivated in B-cells in germinal centres.	(89)
-18.7	Dnm1l	dynamin 1-like	Dynamin-like GTPase (Drp1/ Dlp1): a mechanoenzyme that uses GTP hydrolysis to power mitochondrial and peroxisomal fission. Implicated in apoptosis and energy metabolism.	(90)
-9.1	Abcb9	ATP-binding cassette, sub-family B (MDR/TAP), member 9	Also called TAPL (TAP-like): functions in antigen-processing. Is an ATP-dependent peptide transporter localised to lysosomes. Not regulated by IFN-g and not part of the classical MHC-I pathway. Postulated to act in the cross-presentation pathway. Could also function in removal of cellular debris.	(91)
-7.5	Cul4a	cullin 4A		
-5.3	Tmlhe	trimethyllysine hydroxylase, epsilon		
-4.7	D4Wsu53e	DNA segment, Chr 4, Wayne State University 53, expressed		
-4.1	2900097C17Rik	RIKEN cDNA 2900097C17 gene		
-2.6	Cd4	CD4 antigen	MHC-II co-receptor. Marker of Th1 and Th2 cells.	
-2.5	Tgfbr2	transforming growth factor, beta receptor II	Involved in cell growth, differentiation, immunosuppression, homeostasis and apoptosis.	
-2.1	Shc1	src homology 2 domain-containing transforming protein C1	Signalling molecule activated upon TCR engagement. Involved in thymocyte development	(92, 93)
-2	Cxcl10	chemokine (C-X-C motif) ligand 10	Produced predominantly by Th1 cells, induced by IFN-gamma, binds to CXCR3, involved in chemoattraction of monocytes and T-cells.	
-2	Pfn2	profilin 2	Regulates endocytosis and competes with ligand binding to dynamin 1.	
-2	S100a8	S100 calcium binding protein A8	See S100a8 above	
-2	Tapbp	TAP binding protein	Also called Tapasin. Inolved in MHC-I antigen presentation pathway; part of the peptide-loading complex.	
-2	Pecam	platelet/endothelial cell adhesion molecule	Pecam/CD31: implicated in leukocyte extravasation	
-1.9	Tcrb-J	T-cell receptor beta, joining region	A segment of the T-cell receptor beta gene locus.	
-1.9	Cd86	CD86 antigen	CD86/B7.2 - provides a co-stimulatory signal for T cell activation and survival. Binds to CD28. CD86 and CD80 provide the necessary stimuli to prime T cells for antigen presentation.	
-1.9	Cd8a	CD8 antigen, alpha chain	MHC-I co-receptor. Marker of cytotoxic T-cells.	
40.7	Lipf	lipase, gastric		
7.1	BC037006	cDNA sequence BC037006		
6.6	Dmbt1	deleted in malignant brain tumors 1	A scavenger receptor (pattern recognition receptor), alternatively spliced to make 2 mucosal defence molecules: gp-340 and agglutinin. Upregulated in inflammation.	(94)
6.3	U46068	cDNA sequence U46068		
6	Enpp3	ectonucleotide pyrophosphatase/ phosphodiesterase 3	(CD203c) A basophil-specific ectoenzyme; marker of activation	

The gene list was truncated to include those with >4-fold altered expression, and/or previously-demonstrated roles in mucosal or systemic immunity. FC = fold change. *(A full gene list is available from the authors upon request.)*

unravelling the relative contributions of these cytokines and their associations with downstream and upstream immunological events in host protection against oral candidiasis. Our future directions in elucidating these mechanisms are based on experimentally-confirmed data and also putative host response pathways as summarised in Figure 1.

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Abbreviations: AIDS, acquired immune deficiency syndrome; CMC, chronic mucocutaneous candidiasis; CMI, cell-mediated immunity; CR3, complement receptor 3; DC, dendritic cell; DC-SIGN, dendritic cell-specific intercellular adhesion molecule 3 grabbing nonintegrin; GM-CSF, granulocyte macrophage colony-stimulating factor; HAART, highly activity anti-retroviral therapy; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; Jak, janus kinase; MHC, major histocompatibility complex; NF-kappaB, nuclear factor-kappa B; NK, natural killer; OEC, oral epithelial cell; PAMP, pathogen-associated molecular pattern; Stat, signal transducers and activators of transcription; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumour necrosis factor; Treg, regulatory T-cell

Key Words: fungus, oral, Th1, Th17, Interleukin-12, Interleukin-17, Interleukin-23, *Candida albicans*, Thrush, Host Response, Review

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