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Cytokines and the regulation of fungus-specific CD4 T cell differentiation

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Abstract

CD4 T cells play important and non-redundant roles in protection against infection with diverse fungi. Distinct CD4 T cell subsets can mediate protection against fungal disease where Th1 and Th17 CD4 T cell subsets have been found to promote fungal clearance and protective immunity against diverse fungal pathogens. The differentiation of naïve CD4 T cells into Th1 or Th17 cells is crucially controlled by their interaction with dendritic cells and instructed by cytokines. IL-12 and IFN- γ promote Th1 differentiation while TGF- β , IL-6, IL-1, IL-21 and IL-23 promote Th17 differentiation and maintenance. The production of these cytokines by DCs is in turn regulated by innate receptors triggered in response to fungal infection. In this review we will discuss the contributions of cytokines found to influence fungus-specific CD4 T cell differentiation and their role in defense against fungal disease. We will also highlight the contributions of innate receptors involved in recognition of fungi and how they shape cytokine secretion and CD4 T cell differentiation.

Keywords

CD4 T cell differentiation; Fungal Infection; Innate receptors; Th1; Th17

Introduction

CD4 T cells are a crucial component of the immune response to fungal pathogens. The essential role of CD4 lymphocytes in conferring protection from infection with diverse fungal pathogens is demonstrated by enhanced susceptibility to fungal infections in HIV infected patients. Progressive loss of CD4 T cells leads to increased susceptibility to *Cryptococcus*, *Histoplasma*, *Aspergillus*, *Candida* and *Pneumocystis*[1]. Similarly, mouse models of fungal infection have documented an essential role for CD4 T lymphocytes in protection from fungal disease[2–13]. The contribution of CD4 T cells to antifungal immunity is further suggested by the possibility of conferring CD4 T cell-mediated vaccine protection against diverse fungi in mouse models of fungal disease[2, 14–19]. The protective

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capacity of CD4 T cells is largely mediated by the secretion of distinct cytokines that orchestrate an effective response. In the context of various fungal infections CD4 T cells of the Th1 or Th17 lineages mediate protection from fungal disease[18, 20–32]. In contrast, Th2 cells have been found to play a detrimental role in most experimental models of fungal disease[33–36]. The classification of CD4 T cells as Th1 or Th17 is based largely on the cytokine secretion profile of the cells, thus Th1 cells are characterized by the secretion of IFN- γ , TNF- α , GM-CSF while Th17 are distinguished as producers of IL-17A, IL-17F and IL-22. The effector function of each lineage is differentially mediated by the effects of the unique cytokines produced by each subset. The acquisition of a distinct cytokine profile by naïve CD4 T cells is largely dependent on the interaction with dendritic cells and modulated by cytokines produced by DCs and other innate cells early after infection. Th1 CD4 T cell differentiation is instructed by the actions of IL-12 and IFN- γ that lead to the expression of the Th1-lineage specification transcription factor T-bet [37, 38]. Th17 cells are similarly induced by the activities of various cytokines including TGF- β , IL-6, IL-1, IL-21[37, 39]. Th17 differentiation and maintenance in vivo is dependent on IL-23 and selective depletion of IL-23R in T cells leads to diminished Th17 differentiation[40, 41]. The transcription factors ROR γ t and ROR α are required for Th17 differentiation and for the expression of the Th17 signature cytokines[42, 43]. Th2 cell differentiation depends on the activities of IL-4 and the transcription factor GATA3[37]. Differentiation into each lineage is also opposed by cytokines thus IFN- γ promotes Th1 while suppressing Th2 and Th17 development, IL-4 promotes Th2 and suppresses Th1 and Th17 while TGF- β promotes Th17 and suppresses Th1 and Th2 cell differentiation[37, 44]. Thus, cytokines are important not only as mediators of CD4 T cell effector functions but also in the instruction of CD4 T cell lineage acquisition. In this review we will discuss cytokines found to be important in instructing fungus-specific CD4 T cell differentiation with a focus on Th1 and Th17 lineage decisions and how recognition of fungi by innate receptors regulate their expression and fungus-specific CD4 T cell differentiation.

Cytokines and the regulation of Th1 differentiation

Interleukin 12

The crucial role of IL-12 in shaping CD4 T cell differentiation is well established and for more than a decade IL-12 has been considered as the critical cytokine that links innate and adaptive immunity. IL-12 is a heterodimeric cytokine composed of IL-12p35 and IL-12p40 polypeptides that form the bioactive IL-12p70. The heterodimer binds to the IL-12 receptor composed of IL-12R β 1 and IL-12R β 2 chains and signals through STAT-4[45, 46]. IL-12 is primarily secreted by dendritic cells and acts on NK cells to promote IFN- γ secretion and on naïve CD4 T cells to direct Th1 differentiation. In the absence of IL-12p35 or IL-12p40 mice display enhanced susceptibility to infection with *Cryptococcus*, *Blastomyces* and *Candida* [19, 32, 47, 48]. Similarly, mice treated with blocking antibodies against IL-12p40 are more susceptible to infection with *Histoplasma*[49]. Although IL-12p40 is shared by both IL-12p70 and IL-23 the importance of IL-12p70 in mediating defense against fungal infection is further suggested by studies where administration of recombinant IL-12p70 promoted fungal clearance and reversal of susceptibility of IL-12p40^{-/-} mice[19, 48–50]. Moreover, patients with genetic disorders on IL-12 receptor are more susceptible to *Coccidioides* and *Paracoccidioides* fungal infections further highlighting the importance of IL-12 in immunity to fungi[51, 52]. In the absence of IL-12 production, IFN- γ secretion is greatly diminished and Th1 differentiation is impaired[53, 54]. Thus the requisite role for IL-12 in defense against fungal infection is tightly linked to its ability to influence IFN- γ production and CD4 T cell differentiation towards the Th1 lineage.

In the context of *Aspergillus fumigatus* infection, IL-12 mediates a protective effect against invasive fungal disease and was found to promote protective Th1 CD4 T cell differentiation

[2, 16]. During *A.fumigatus* infection, IL-12 plays a non-redundant role in promoting Th1 differentiation while constraining Th17 development [55]. The ability of IL-12 to influence Th1 versus Th17 differentiation is linked to T-bet induction and in the absence of IL-12p35, *A.fumigatus*-specific CD4 TCR-tg cells (Af3.16 TCR-tg) are unable to acquire T-bet expression [55]. T-bet acts in a T cell intrinsic manner to constrain Th17 development and T-bet-deficient, *A.fumigatus*-specific CD4 T cells differentiate into IL-17A-producing Th17 cells in contrast to the dominant Th1 differentiation of wild type Af3.16 TCR-tg cells [55, 56]. The impact of IL-12 on T-bet induction is likely mediated through its effect on IFN- γ expression although there is evidence of direct induction of T-bet by IL-12 [57]. In addition to promoting Th1 differentiation via effects on T-bet, IL-12 can promote a complete Th1 differentiation program independently of T-bet through direct effects of STAT-4[58]. It has also been reported that IL-12 can modulate antifungal responses in innate cells independently of its effects on IFN- γ raising the possibility of multiple antifungal effects of IL-12[59].

IFN- γ

Interferon gamma, or type II interferon, is a pleotropic cytokine that confers protection against a variety of fungal infections[17, 21, 60–66]. IFN- γ is made of a homodimer that binds to its unique receptor composed of IFNGR1 and IFNGR2 chains. Signaling through the IFN- γ receptor leads to STAT-1 activation and multiple biological activities including activation of antimicrobial activity of phagocytes, increased antigen processing and MHC expression, activation of iNOS and induction of T-bet and Th1 differentiation. The important role of IFN- γ in defense against fungi is highlighted by the susceptibility of IFN- γ -deficient mice to infection with *Histoplasma*, *Cryptococcus*, *Blastomyces* and *Candida* and by the beneficial effect of exogenous IFN- γ administration to patients with invasive fungal disease[21, 60–62, 64, 66–68]. IFN- γ is the hallmark cytokine produced by Th1 CD4 T cells and it also plays an important role in directing Th1 CD4 T cell differentiation while suppressing alternative Th2 and Th17 programs. IFN- γ signals are propagated by STAT-1 which promotes T-bet and IL-12R β 2 expression in responding CD4 T lymphocytes. Innate production of IFN- γ is largely derived from NK cells although DCs can also produce INF- γ upon TLR stimulation[69–73]. DCs also contribute to innate production of IFN- γ by NK cells through the secretion of TLR-induced IL-12 production. Early during *A.fumigatus* infection NK cells can be the primary source of innate IFN- γ and can mediate direct antifungal effects against *A.fumigatus*-hyphae[72, 74, 75]. Release of IFN- γ by NK cells can also be induced by *Cryptococcus* and *Candida*[71].

During *A.fumigatus* infection IFN- γ is an essential factor for Th1 differentiation and in its absence *A.fumigatus*-specific CD4 T cell fail to upregulate T-bet[55]. Absence of IFN- γ leads to limited Th1 differentiation and enhanced Th17 differentiation. The same was observed in IL-12p35-deficient mice indicating that both IFN- γ and IL-12 are essential in promoting fungus-specific CD4 T cell differentiation while inhibiting Th17 cells[55].

Type I interferon

Type I interferons are classically associated with viral infection and are group of closely related cytokines including multiple IFN- α subtypes, IFN- β , IFN- ω and IFN- τ all which bind a common IFNAR receptor composed of IFNAR1 and IFNAR2 chains[76, 77]. Signaling through IFNAR leads to the formation of STAT-1/STAT-2 heterodimers and STAT-1 homodimers. It is also possible for IFNAR signals to induce STAT-4 activation and to influence CD4 T cell differentiation[76–78]. Although type I interferons can be produced by any cell type in the body, plasmacytoid DCs are specially capable of secreting large amounts of type I interferon and are the first source of these cytokines in response to viral infection[79]. Recent studies have demonstrated that type IFNs are also involved in

antifungal immunity and can be produced by DCs in response to fungal stimulation[80–83]. Moreover, plasmacytoid DCs were recently identified as crucial in mediating defense against *A.fumigatus* infection and IFNAR deficient mice were more susceptible to aspergillosis[84]. Type I interferons have also been found to mediate defense against *Candida* infection with IFN- α/β receptor deficient mice displaying enhanced susceptibility to infection[81]. Type I interferons are also induced after infection with *Histoplasma* conidia and mediate defense against *Cryptococcus* infection[80, 83]. In the context of *Pneumocystis* infection, type IFNs are involved in control of inflammation in the lung and are required for the regeneration of hematopoietic cells after infection[85–87]. Thus type I interferons are not only involved in anti-viral responses but contribute to defense against diverse fungal pathogens. In the context of viral infection type I interferons were found to promote Th1 differentiation via activation of STAT-4 although other studies did not detect a long lasting effect of type I interferon stimulation on T-bet expression and have questioned the involvement of type I interferons in promoting Th1 differentiation in vivo[78, 88]. In vitro studies suggest that IFN- β conditioned DCs promote *A.fumigatus*-specific Th1 CD4 T cells thus suggesting a possible role for type I interferons in shaping fungus-specific Th1 differentiation but further studies will be needed to determine the exact contribution of Type I interferons on fungus-specific CD4 T cell differentiation[89]. A possible role for type I interferons in shaping pathogen-specific CD4 T cell differentiation is suggested by recent studies on immunization models or bacterial infection where abrogation of type I interferon responsiveness by deletion of IFNAR resulted in limited Th1 differentiation[80, 90, 91].

Cytokines that promote Th17 differentiation

IL-23

IL-23 is a heterodimeric cytokine that belongs to the IL-12 family and it is composed of the unique IL-23p19 polypeptide and the shared IL-12p40 subunit. The IL-23 receptor is composed of the shared IL-12R β 1 chain and unique IL23R chains and signals through STAT-3 activation[92]. The identification of IL-23 as a new member of the IL-12 family of cytokines facilitated the identification of Th17 as a distinct lineage of CD4 T cells[40, 93, 94]. Studies comparing IL-12p35 and IL-12p40 deficient animals had shown discrepancies where IL-12p40^{-/-} mice were frequently found to be more susceptible to infection than IL-12p35^{-/-} mice. These findings were hard to reconcile if both components formed only one cytokine. The identification of IL-12p40 as a shared subunit between two cytokines clarified some of those observations and suggested an important role for IL-23 as another innate cell-derived cytokine with the capacity to shape CD4 T cell differentiation. Although IL-23 is not required for Th17 differentiation in vitro it is an essential factor for in vivo maintenance of Th17 cells and IL23p19^{-/-} mice show limited IL-17 production in response to fungal infections[31, 40, 95, 96]. In response to fungal infection, IL-23 has been found to play a protective role by promoting IL-17 production and enhanced fungal clearance. Mice deficient in IL-23p19 display higher fungal burden upon infection with *Histoplasma*, *Cryptococcus*, *Pneumocystis* and *Candida*[29, 31, 95, 96]. In contrast, studies in pulmonary *Aspergillus* infection and gastric *Candida* found a detrimental role for IL-23/IL-17 axis by promoting excessive neutrophil inflammation and tissue destruction[97]. Thus, IL-23 can mediate protection against fungal infection but may also be detrimental in promoting excessive inflammation similar to its role in autoimmune diseases.

IL-17A

IL-17A is a homodimeric cytokine that binds the IL-17R receptor complex IL17RA and IL-17RC. Signaling through IL17R requires TRAF6 and promotes the production of pro-inflammatory cytokines, chemokines and antimicrobial peptides including IL-6, GM-CSF, CXCL1, CXCL5 and β -defensin[98, 99]. The capacity of IL-17A to promote neutrophil

recruitment is central to its role in defense against infection. IL-17A is the hallmark cytokine produced by Th17 cells and its transcription is induced by the Th17-specification transcription factors ROR γ t and ROR α [42, 43]. Although IL-17A is mostly associated as a signature of Th17 cells, other T cell subsets can also produce it including NKT cells and $\gamma\delta$ T cells[100–103]. These innate populations can produce large amounts of cytokine early after infection and have been identified as an important source of IL-17A. The production of IL-17 by innate cell populations is reminiscent of IFN- γ which is the hallmark effector cytokine of Th1 cells and it is also produced by NK cells early after infection at the onset of CD4 T cell differentiation. IL-17A has been found to function as a crucial cytokine in defense against diverse fungal infections[25, 28–31, 95, 104, 105]. Mice deficient in IL-17A, IL17RA or treated with neutralizing antibodies display enhanced fungal burden and susceptibility to *Candida*, *Blastomyces* and *Histoplasma*[18, 25, 28, 29, 95, 106]. There is also some experimental evidence for a positive effect of IL-17 in *Pneumocystis* and *Cryptococcus* infection[27, 31, 32]. The role of IL17A in defense against *Aspergillus* infection appears to be more complex. Lower levels of IL-17 secretion have been associated with enhanced fungal burden thus suggesting a protective role for IL-17 especially through the recruitment of neutrophils which mediate important and non-redundant function in preventing invasive fungal growth[107, 108]. In contrast, mouse models of invasive aspergillosis reported a role for IL-17 and IL-23 in excessive tissue damage with a detrimental role for IL-17A[97]. Similarly, in a mouse model of *Aspergillus* susceptibility in chronic granulomatous disease (CGD), excessive IL-17A production by $\gamma\delta$ T cells was a crucial mediator of tissue damage and mortality[102].

In humans IL-17A is an important factor in defense against fungal disease especially against *Candida*[109]. Patients with STAT-3 defects suffer from autosomal dominant hyper IgE syndrome (HIES) and show enhanced susceptibility to fungal infection[110, 111]. Defective STAT-3 signaling was found to contribute to impaired Th17 differentiation further suggesting the important contribution of IL-23/STAT-3 (as well as other STAT-3 activating cytokines) in Th17 differentiation and activation of antifungal immunity. A role for IL-17 and Th17 CD4 T cells in defense against fungal infection is further suggested by the observation that in some CMC patients autoantibodies against IL-17A, IL-17F and IL-22 underlie susceptibility to infection[112, 113]. Thus there is extensive evidence from mouse models and clinical studies to support an important role of IL-17A in defense against fungal infections. On the other hand, IL-17 can be detrimental in autoimmune disease and under specific circumstances can also be detrimental in the context of fungal infection.

IL-22

IL-22 is a member of the IL-10 family of cytokines and shares the IL-10R2 signaling receptor chain with IL-10 and other family members. It is produced primarily by Th17 cells but dendritic cells and NK cell subsets can also secrete it [114]. A role for IL-22 in defense against fungal infection is suggested by the observation that some patients with CMC produce anti-IL-22 antibodies in addition to anti-IL17[113, 115, 116]. Mouse studies also revealed that IL-22 can mediate protective effects against fungal infection in the absence of adaptive immunity[115]. Similar to IFN- γ and IL-17, IL-22 is not only produced by CD4 T cell subsets but also by innate cells in response to microbial stimuli thus suggesting distinct effects of this cytokine at various times after fungal infection.

Regulation of cytokine production by innate receptors

Toll-like receptors (TLRs) and Dectin-1

Cell wall components of most fungi can be recognized by TLR-2, TLR-4 and TLR-9 and trigger the activation of dendritic cells and secretion of cytokines [117, 118]. TLRs are

involved in immunity to many pathogens and have been found to influence adaptive immunity by mediating the adjuvant effects of LPS (TLR-4 agonist) and CpG (TLR-9)[119]. The exact components of fungal cell walls or fungal DNA recognized by TLR-2 and 4 or TLR-9 respectively are not currently known but many studies have documented TLR-dependent activation of DCs by several fungal pathogens[118, 120–124]. Studies in mice have documented enhanced susceptibility to fungal infection in mice deficient in MyD88 (common signaling adaptor of TLRs 2,4 and 9) further suggesting a role for TLRs in defense against fungal infection[125–127]. Moreover, polymorphisms in TLR4 have been associated with enhanced susceptibility to invasive aspergillosis in patients undergoing bone marrow transplantation[128, 129].

The non-TLR innate receptor Dectin-1, recognizes β -(1,3) glucan on the surface of many fungi and promotes phagocytosis, production of reactive oxygen species (ROS) and cytokine secretion[130–133]. Dectin-1 signals through Syk-CARD9 and Raf-1 kinase leading to the activation of canonical and non-canonical NF κ B pathways[134–137]. The importance of Dectin-1 in defense against fungal infection is demonstrated by the enhanced susceptibility of Dectin-1^{-/-} mice to *Candida*, *Pneumocystis* and *Aspergillus* infection[107, 138, 139]. Moreover, patients with defects in Dectin-1 and CARD9 have been found to suffer from CMC and polymorphisms in Dectin-1 were associated with enhanced susceptibility to IA in bone marrow transplanted patients[140–143].

TLRs and Dectin-1 innate receptors influence fungus-specific CD4 T cell differentiation via the differential induction of cytokine secretion on dendritic cells especially of members of the IL-12 family[45]. Triggering of Dectin-1 and TLRs leads to the synergistic production of TNF and chemokines MIP-1 α and MIP-2 by dendritic cells in a Syk-dependent manner[144, 145]. In contrast, co-ligation of Dectin-1 and TLR2- leads to diminished IL-12p35 transcription and enhanced IL-23p19 therefore tipping the balance of T cell differentiation in favor of Th17 cells[146]. Various studies have suggested the contribution of Dectin-1 to Th1 and Th17 differentiation and Dectin-1^{-/-} mice were found to produce limited amounts of IL-17 upon *A.fumigatus* infection[55, 107, 147–149]. Dectin-1 signals through Syk-CARD9 axis and patients with defects in Dectin1 or CARD-9 show limited production of IL-17 and low frequencies of Th17 cells[142, 143]. Various studies have shown that Dectin-1-dependent production of IL-23 is linked with the capacity of this receptor to promote Th17 responses[146, 147, 149].

Dectin-2

The role of Dectin-1 in defense against fungi is not universal and mice deficient in Dectin-1^{-/-} are resistant to infection with *Blastomyces*, *Cryptococcus* and certain strains of *Candida*[18, 138, 150]. Similarly, patients with Dectin-1 defects do not seem to be at higher risk for invasive fungal disease[142]. The observation that CARD9 deficient patients suffer from more severe fungal infections than those observed in patients with Dectin-1 defects further suggests the contributions of other innate receptors with the capacity to stimulate CARD9. Indeed, Dectin-2 has been shown to stimulate Syk/CARD9 via its interaction with Fc γ receptor[134, 151–153]. Dectin-2 can recognize α -mannans and has been shown to play a non-redundant role in defense against *Candida* infection[152, 153]. Similar to Dectin-1, Dectin-2 was found to favor Th17 differentiation in response to *Candida*[152, 153]. α -mannans are present in the cell wall of many fungi and thus it is likely that Dectin-2 might be involved in the antifungal response of other fungi. Interestingly, Dectin-2 has been found to shape Th2 differentiation in asthma models further suggesting a contribution for Dectin-2 in shaping CD4 T cell differentiation[154].

Distinct contributions of MyD88 and Dectin-1 to fungus-specific CD4 T cell differentiation

In vivo studies of fungus-specific CD4 T cell differentiation in response to *A.fumigatus* infection revealed that Dectin-1 signals not only serve as a positive factor to promote Th17 differentiation but rather act to balance Th1 versus Th17 differentiation[55]. By exploiting the development of *A.fumigatus*-specific CD4 TCR-tg mice we were able to dissect the exact contributions of TLR/MyD88 and Dectin-1 to fungus-specific CD4 T cell differentiation. In the absence of Dectin-1, Af3.16 TCR-tg cells display enhanced Th1 differentiation and limited IL-17 secretion. Thus, we reasoned that Dectin-1 signals promote Th17 differentiation by suppressing Th1 differentiation. Expression of T-bet by Af3.16 TCR-tg cells was a critical determinant in Th1 versus Th17 differentiation and Dectin-1 signals acted to modulate the levels of this crucial transcription factor in vivo. Innate production of IFN- γ and IL-12 were augmented in Dectin-1-deficient mice thus suggesting that Dectin-1 signals diminish the production of these cytokines. Indeed both IFN- γ and IL-12 were required to maintain *A.fumigatus*-specific Th1 differentiation and in their absence Af3.16 TCR-tg cells failed to upregulate T-bet and showed Th17 skewing. These findings further highlight the contribution of IL-12 and IFN- γ in preventing Th17 differentiation while promoting Th1 responses.

MyD88 signals favor Th1 differentiation and in response to *A.fumigatus* infection, MyD88 signals contribute to T-bet induction in the lymph node and fungus-specific CD4 T cells primed in MyD88^{-/-} mice show limited IFN- γ production in the lung[56]. Interestingly, CD4 T cell activation and proliferation in the lung-draining lymph node is preserved in mice deficient in MyD88 and Dectin-1 suggesting the important contributions of other innate receptors to DC maturation and CD4 T cell priming[55]. Further studies will be needed to dissect the specific contributions of other innate receptors in shaping fungus-specific CD4 T cell activation and differentiation. The contribution of other innate receptors is also suggested by preserved CD4 T cell activation and Th1 differentiation observed in Dectin-1^{-/-}MyD88^{-/-} mice implying the involvement of other innate receptors with the capacity to mediate fungus-specific CD4 T cell activation, recruitment to the lung and Th1 differentiation[55].

In contrast to the minimal requirement for MyD88 in *A.fumigatus*-specific CD4 T cell activation and differentiation, studies with *Blastomyces*-specific CD4 TCR-tg cells revealed that CD4 T cell response to this fungus are completely dependent on MyD88[18]. Using a vaccination strategy, Wuthrich, et al demonstrated that in the absence of MyD88, protective CD4 T cell responses were severely impaired[18]. In contrast, Dectin-1^{-/-} mice were fully protected after vaccination indicating that Dectin-1 signals were not required for *Blastomyces*-specific CD4 T cell activation and differentiation[18]. These findings are in contrast with those observed in *A.fumigatus* system and are very likely due to the different composition of cell wall components of these fungi and their differential capacity to activate innate receptors. The differences in these studies highlight the importance of probing immune defense mechanisms against various fungi to better inform future vaccine development against diverse fungal pathogens. Future studies will likely reveal more surprises about the specific contribution of cytokines to fungus-specific CD4 T cell activation and how the interaction of innate receptors both agonistic and antagonistic may shape adaptive immunity to fungi.

Concluding remarks

Vaccine development against fungi has been an unfulfilled promise for several decades but recent studies give reason for hope. The identification of a CD4 T cell clone with the capacity to confer protection against diverse dimorphic fungi suggest the possibility of developing novel vaccines that could confer cross-protection against various fungi[18, 155].

Similarly, recent studies identified shared CD4 T cell responses in humans against *A.fumigatus* and Candida antigens also suggesting the possibility of inducing cross protective immunity against fungi by vaccination[156]. A detailed understanding of how innate receptors shape cytokine secretion and the distinct contributions of such cytokines to CD4 T cell activation, trafficking and differentiation will be crucial for the targeted development of novel vaccines and therapeutic interventions against the rising contribution of fungal disease to mortality in diverse patient populations.

Highlights

- * Cytokines are crucial in instructing fungus-specific CD4 T cell differentiation
- * CD4 T cells of Th1 and Th17 lineages are crucial for defense against fungal infection
- * Innate receptors shape CD4 T cell differentiation by modulation of cytokine secretion
- * Th1 versus Th17 differentiation is critically controlled by IFN- γ and IL-12
- * IL-12, IFN- γ , Type IFNs, IL-23, IL-17A and IL-22 promote antifungal immunity

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