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Insights from human studies into the host defense against candidiasis

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Abstract

Candida spp. are the most common cause of mucosal and disseminated fungal infections in humans. Studies using mutant strains of mice have provided initial information about the roles of dectin-1, CARD9, and Th17 cytokines in the host defense against candidiasis. Recent technological advances have resulted in the identification of mutations in specific genes that predispose humans to develop candidal infection. The analysis of individuals with these mutations demonstrates that dectin-1 is critical for the host defense against vulvovaginal candidiasis and candidal colonization of the gastrointestinal tract. They also indicate that CARD9 is important for the preventing both mucosal and disseminated candidiasis, whereas the Th17 response is necessary for the defense against mucocutaneous candidiasis. This article reviews the recent studies of genetic defects in humans that result in an increased susceptibility to candidiasis and discusses how these studies provide new insight into the host defense against different types of candidal infections.

Keywords

Dectin-1; CARD9; Th17; *Candida*; Host defense

1. Introduction

The fungus *Candida* spp. usually grows as a harmless commensal on mucosal surfaces. However, when there is a perturbation of either local or systemic defense mechanisms, this organism can proliferate and cause superficial infections such as oropharyngeal and vulvovaginal candidiasis. Furthermore, in hospitalized patients *Candida* spp. can enter the bloodstream via an indwelling vascular catheter or translocation across the gut and cause hematogenously disseminated candidiasis, a disease that remains associated with significant mortality even with current therapy.

Because *Candida* spp. are opportunistic pathogens that rarely causes disease in immunocompetent individuals, it is important to understand both the host defense mechanisms that normally prevent candidal infections and the immune defects that enable

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these infections to occur. This knowledge holds promise to lead to better approaches to prevent and treat candidiasis.

Until recently, most insight into the host defense against candidal infections was obtained from mouse experiments. While mouse models are extremely useful for investigating the immune response to candidiasis, there are some notable differences between the mouse and human immune system. For example, in mice the main neutrophil chemoattractants are KC, MIP1 α and MIP1 β , whereas in humans IL-8 is the principal neutrophil chemoattractant. Also, murine macrophages kill *Candida albicans* via the release of large amounts of nitric oxide. In contrast, human macrophages make little nitric oxide and kill *C. albicans* by reactive oxygen intermediates [1]. Furthermore, mice are resistant to *C. albicans* colonization of mucosal surfaces unless they are administered antibiotics, whereas at least 50% of normal humans are colonized with this organism. Because of these differences, murine studies of the host defense against candidiasis provide incomplete insight into human immunity.

Within the past few years, the development of new technologies, such as next generation genome sequencing has led to the discovery of specific genetic mutations in humans that result in increased susceptibility candidal infections. These fascinating studies have shed new light on the receptors, cytokines, signaling pathways, and effectors that are operative in the host defense against candidiasis in humans. Here, we will review these investigations.

2. Dectin-1

Dectin-1 is a C-type lectin receptor that recognizes β -glucans, such as those present in the cell wall of *Candida* spp. This receptor is expressed on both myeloid cells and some types of epithelial cells [2, 3]. Importantly, the distribution of dectin-1 is different in mice and humans. For example this receptor is expressed on B cells and eosinophils of humans, but not mice [2]. Murine studies of the role of dectin-1 in the host defense against *C. albicans* have yielded conflicting results. One group found that a *DECTIN-1*^{-/-} mouse strain had increased susceptibility to lethal disseminated candidiasis [4]. In contrast, another group, using an independently constructed *DECTIN-1*^{-/-} mouse strain, found that dectin-1 was dispensable for the host defense against disseminated candidiasis [5]. Subsequently, it was found that the reason for these discrepant results was due differences in the *C. albicans* strain that was used to inoculate the mice [2]. Thus, murine studies have not provided a clear picture about the role of dectin-1 in the host defense against disseminated candidiasis.

In contrast, mouse studies on the contribution of dectin-1 to the host defense against gastrointestinal colonization have yielded concordant results. One group found that when *DECTIN-1*^{-/-} mice were inoculated with *C. albicans* intravenously, they had high levels of this organism in their gastrointestinal tract, suggesting that dectin-1 may be required for the host defense against gastrointestinal colonization [4]. Using macrophage-specific *DECTIN-1*^{-/-} mice and a different strain of *C. albicans*, another group of investigators also found that mice lacking dectin-1 had significantly increased gastrointestinal fungal burden following oral inoculation with *C. albicans* [6]. Therefore, murine studies suggest that dectin-1 plays an uncertain role in the host defense against disseminated candidiasis, but appears to be important for preventing gastrointestinal colonization.

Recently, it has been discovered that humans have a naturally occurring premature stop codon Tyr238X mutation in dectin-1 that results in a receptor that is non-functional and expressed at very low levels on the cell surface. This mutation has an allele frequency of 0.023 to 0.07 in various populations [7]. The investigation of individuals with this polymorphism has provided the unique opportunity to determine the role of dectin-1 in the host defense against candidal infections in humans.

The first report of functional dectin-1 deficiency described a family in which three sisters were homozygous for the Tyr238X mutation [7]. All of these women had either chronic or recurrent onychomycosis and two of them had recurrent vulvovaginal candidiasis [7]. These results suggested that in humans, dectin-1 plays a key role in the host defense against onychomycosis and vulvovaginal candidiasis. However, the frequency of the Tyr238X mutation in patients with either of these diseases has not been determined, so it is not yet clear what proportion of patients are susceptible to onychomycosis or vulvovaginal candidiasis because of this mutation. It was also interesting that the patients who were homozygous for the dectin-1 Tyr238X mutation did not develop oropharyngeal candidiasis, a result that reinforces the concept the mechanisms of host defense against candidal infection differ at different mucosal sites.

Subsequently, it was determined that patients with a hematologic malignancy who were heterozygous for the Tyr238X mutation were significantly more likely to have oral and/or fecal colonization with *Candida* spp. compared to patients who did not have this polymorphism [8]. However, when these patients underwent hematopoietic stem cell transplantation, the incidence of candidemia was not significantly influenced by the presence of the Tyr238X polymorphism [8]. These results suggested that dectin-1 is important for the prevention of candidal colonization of the gastrointestinal tract, but not for the host defense against disseminated candidiasis. The lack of association between the Tyr238X mutation and susceptibility to candidemia was verified by another study that compared the frequency of this mutation in 331 patients with candidemia and 351 matched controls [9]. Furthermore, patients with the Tyr238X mutation who developed candidemia did not have increased mortality compared to patients without this mutation, indicating that the mutation did not have a significant effect on treatment outcome. A caveat to this study is that none of the patients with candidemia were homozygous for the Tyr238X mutation. Thus, while it is clear that a partial deficiency in dectin-1 does not result in significantly increased susceptibility to disseminated candidiasis, it remains possible that patients with complete deficiency of dectin-1 might have greater susceptibility to this disease.

A study of HIV-infected Tanzanian patients examined the role of polymorphisms in innate immune genes in susceptibility to oropharyngeal candidiasis. They found that the frequency of the Tyr238X allele was too low in these patients to draw conclusions about its influence on susceptibility to this disease. However, they found that the Ile223Ser allele of *DECTIN-1* was almost 2-fold more prevalent in the patients who did not develop oropharyngeal candidiasis, a trend that did not quite achieve statistical significance [10]. Dectin-1 with the Ile223Ser mutation has reduced surface expression and β -glucan binding, which results in lower production of IFN- γ in response to ligand binding. The authors speculated that the reduced functionality of this mutated dectin-1 was protective against oropharyngeal candidiasis because it was associated with decreased T cell activation and therefore lower HIV replication. Nevertheless, it is clear that maximal dectin-1 function is not required for the host defense against oropharyngeal candidiasis in humans.

Collectively, these studies indicate that in humans, dectin-1 is dispensable for the host defense against disseminated candidiasis or oropharyngeal candidiasis. However, it appears to be critical for reducing susceptibility to gastrointestinal colonization and vulvovaginal candidiasis.

3. CARD9

Dectin-1 and other C-type lectins, such as dectin-2 and macrophage-inducible C-type lectin (Mincle) transmit signals through a protein complex that contains caspase recruitment domain 9 (CARD9) [11, 12]. This signaling complex activates NF κ B and mitogen-activated

protein kinases [12]. *CARD9*^{-/-} mice have markedly increased susceptibility to disseminated candidiasis [11, 12]. However, their susceptibility to mucosal candidiasis has not yet been determined.

A study of humans with *CARD9* deficiency demonstrates that this protein is important for the host defense against both mucosal and disseminated candidiasis. Members of a large, consanguineous Iranian family were discovered to be homozygous for a Gln295X mutation in *CARD9* [12]. This mutation resulted in the production of a truncated protein that did not transmit signals from dectin-1. All of the homozygous individuals had recurrent oropharyngeal and/or vulvovaginal candidiasis, indicating the importance of *CARD9* in the host defense against these infections. Interestingly, at least two members of the family spontaneously developed fatal candidal meningitis. Although the genotypes of these individuals could not be determined, it is probable that *CARD9* deficiency caused them to develop this unusual infection. Thus, *CARD9* appears to be critical for the host defense against oropharyngeal, vulvovaginal, and disseminated candidiasis, particularly meningitis. It is probable that *CARD9* plays such a central role in the defense against these different types of candidal infections because it transduces the signals of three types of receptors that recognize different cell wall constituents of *Candida* spp.

4. The Th17 response

In 2005, it was discovered that T cells can differentiate into the Th17 phenotype, characterized by the secretion of IL-17A, IL-17F, IL-22, and IL-26 [13–15]. In addition, IL-23 is required to maintain the Th17 phenotype. These cytokines are important for the host defense against infection by augmenting neutrophil recruitment and function, either directly or indirectly. Some of them are also necessary for production of antimicrobial proteins and maintenance of epithelial cell barrier function, as discussed below.

IL-17A can form both a homodimer with itself and a heterodimer with IL-17F. IL-17A and IL-17F homodimers, and the IL-17A/F heterodimer bind to the IL-17A receptor (IL-17RA). Murine studies indicate that IL-17RA is essential for the host defense against disseminated *C. albicans* infection. For example, *IL-17RA*^{-/-} mice with disseminated candidiasis have accelerated mortality, increased organ fungal burden, and reduced neutrophil accumulation in infected organs as compared to wild-type control mice [16]. IL-22 is also necessary for the normal defense against disseminated candidiasis because *IL-22*^{-/-} mice have increased kidney fungal burden following intravenous inoculation with *C. albicans* [17]. Collectively, these data indicate that in mice, an intact Th17 response is important for the host defense against disseminated candidiasis.

A functional Th17 response has also been found to be essential for the host defense against oropharyngeal candidiasis in mice. Wild-type mice are highly resistant to oropharyngeal candidiasis and must be immunosuppressed to induce susceptibility to this disease. It was recently discovered that *IL-23*^{-/-} mice and *IL-17RA*^{-/-} mice develop oropharyngeal candidiasis following oral inoculation without additional immunosuppression [18]. Interestingly, *IL-22*^{-/-} mice develop only mild oropharyngeal candidiasis, suggesting that IL-22 is less important for the host defense against this disease in mice. It was further determined that the *IL-17RA*^{-/-} mice have reduced oral expression of genes encoding antimicrobial proteins, such as β defensin 3 and CCL20. As predicted by the gene expression data, the saliva from the *IL-17RA*^{-/-} mice has reduced anti-*C. albicans* activity [18]. Thus, an additional role of the Th17 response is to stimulate the production of antimicrobial proteins, which contributes to protection against mucosal infection.

The importance of a Th17 response in the host defense against cutaneous candidiasis has also been demonstrated in mice. It was recently discovered that *IL-23*^{-/-} and *IL-17RA*^{-/-}

mice have delayed clearance of *C. albicans* following subcutaneous inoculation with this organism [19]. However, the clearance of *C. albicans* from the skin of IL-22^{-/-} mice is similar to that of wild-type mice.

Some murine data indicate that the Th17 response can promote a pro-inflammatory response that is not only ineffective in clearing fungal infection, but actually makes it worse. This conclusion is based on results from a murine model of gastric candidiasis. It was found IL-23 receptor^{-/-} mice or wild-type mice that had been given a neutralizing anti-IL-23 antibody had reduced susceptibility to gastric *C. albicans* infection [20]. The protective effect of IL-23 deficiency or neutralization was due to an enhanced Th1 response. However, it was subsequently determined that IL-22^{-/-} mice had increased susceptibility to gastric candidiasis [17]. Thus, deficiencies of different Th17 cytokines appear to have varying effects in this mouse model. Nevertheless, it is difficult to extrapolate the results of the gastric candidiasis studies to humans because this disease rarely occurs in patients.

Collectively, these studies indicate that the Th17 response is important for the host defense against disseminated, oropharyngeal, and cutaneous candidiasis in mice. The role of the Th17 response in the defense against gastric candidiasis is variable, depending on the cytokine studied.

It has been known for many years that some individuals have an inherited predisposition to develop candidal infections. Recently, the mutant genes that are responsible for this increased susceptibility have been identified. Most of these mutations result in defects in the Th17 signaling pathway and they provide important insight into the role of the Th17 response in the host defense against candidiasis in humans.

Patients with hyper-IgE syndrome have recurrent mucocutaneous candidiasis, as well as skin abscesses caused by *Staphylococcus aureus*, pneumatoceles, and bony abnormalities. It was discovered that these patients carry heterozygous mutations in the signal transducer and activator of transcription 3 gene (*STAT3*) [21, 22]. These mutant forms of *STAT3* have a dominant negative effect. Patients with the *STAT3* mutations do not produce IL-17 and thus have no Th17 cells [23]. The recurrent mucocutaneous candidal infections in these patients indicate the importance of the Th17 response in the host defense against this infection. In addition, it has been reported that the saliva of patients with hyper-IgE syndrome has reduced levels of the antimicrobial proteins, β defensin-2 and histatins, and therefore decreased candidacidal activity [24]. These results confirm the mouse studies that show that the Th17 response is essential for the normal production of mucosal antimicrobial peptides and the host defense against mucosal candidiasis. On the other hand, patients with hyper-IgE syndrome do not have a significantly increased incidence of disseminated candidiasis, suggesting that the Th17 response is dispensable for preventing this infection in humans.

Chronic mucocutaneous candidiasis is characterized by recurrent candidal infection of the mucous membranes, skin, and nails. Although patients with this disease frequently have an extremely high fungal burden on their skin and mucosal surfaces, their risk of developing disseminated candidiasis is low. Chronic mucocutaneous candidiasis is a heterogeneous disease that has both sporadic and inherited forms. Within the past few years, the genetic defects that cause this disease have been identified. All of these defects result in an impaired Th17 response, thus demonstrating the importance of this response in the host defense against mucocutaneous candidiasis.

Two groups recently discovered that many patients with the autosomal dominant form of chronic mucocutaneous candidiasis have gain of function mutations in *STAT1*. This mutation causes an enhanced response to inhibitors of IL-17 and IL-22 production and results in a reduced Th17 response [25, 26]. One group found that Th1 responses were also

defective in patients with these mutations [26]. A less common form of autosomal dominant chronic mucocutaneous candidiasis was discovered to be due to a mutation in the *IL-17F* gene. The protein encoded by this mutated gene has a dominant negative effect because when it is present in IL17F homodimers or IL17A/F heterodimers, the resulting proteins fail to bind to IL-17RA. Interestingly, although individuals with this mutation have no detectable IL-17F-expressing T cells, they have normal numbers of IL-17A- and IL-22-expressing T-cells [27]. These results suggest that IL-17 may be more important than IL-22 in host defense against mucocutaneous candidiasis in humans, thus mirroring the results from mouse studies.

An investigation of a patient with autosomal recessive chronic mucocutaneous candidiasis found that he had a premature stop codon mutation in the *IL-17RA* gene. The receptor encoded by this gene was not detectable on the patient's cells, and his fibroblasts did not respond to IL-17A, IL-17F, or an IL-17A/F heterodimer [27]. These data further emphasize the role of IL-17 in preventing candidal infections of the mucosa and skin.

A subset of patients with chronic mucocutaneous candidiasis have autoimmune polyendocrinopathy syndrome type I (APS-I). This autosomal recessive disease is caused by a mutation in the autoimmune regulatory gene, *AIRE* that results in the production of pathologic autoantibodies. These autoantibodies cause autoimmune endocrinopathies, especially adrenal insufficiency and hypoparathyroidism. Patients with APS-I have a very high incidence of chronic mucocutaneous candidiasis, but not other infections. Within the past year it was reported that these patients have neutralizing antibodies to IL-17A, IL-17F, and IL-22 [28, 29]. One study found that the titers of antibodies against IL-17F and IL-22 correlated most closely with the presence of chronic mucocutaneous candidiasis, suggesting that these cytokines are particularly important for the host defense against this disease [28]. Autoantibodies against Th17 cytokines were also detected in patients with thymoma who had chronic mucocutaneous candidiasis, thus providing an explanation for why these patients develop this infection [28].

Collectively, the data from patients with chronic mucocutaneous candidiasis demonstrate unequivocally that the Th17 response is essential for the host defense against superficial candidal infections. The finding that patients with impaired Th17 responses are at dramatically increased risk of developing chronic mucocutaneous candidiasis also suggests that a Th17 response does not induce a pathologic, non-protective inflammatory response to candidal infections in humans, as it does in some mouse models. Furthermore, the fact that patients with Th17 defects are at low risk of developing disseminated candidiasis indicates that the Th17 response is dispensable for the host defense against this type of infection.

5. Conclusion

Although mouse models of candidiasis have provided critical information about the host defense against superficial and disseminated candidal infections, the recent human data provide additional insight into these immune mechanisms. They clearly demonstrate the key roles of dectin-1, CARD9, and the Th17 response in preventing mucosal and cutaneous candidal infections. These studies suggest that augmenting the Th17 response may be an effective approach to preventing and treating such infections. On the other hand, approaches to inhibit the Th17 response are being developed to treat various autoimmune diseases. The very high incidence of chronic mucocutaneous candidiasis in patients with defects in the Th17 response suggests that patients who are receiving therapeutic Th17 inhibitors will likely require prophylactic antifungal agents to prevent these infections.

Highlights

- Dectin-1 prevents vulvovaginal candidiasis and candidal colonization of the gut
- CARD9 is important for the preventing both mucosal and disseminated candidiasis
- An intact Th17 response prevents mucocutaneous but not disseminated candidiasis

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References

1. Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. *J Immunol.* 2004; 172:2731–2738. [PubMed: 14978070]
2. Drummond RA, Brown GD. The role of Dectin-1 in the host defence against fungal infections. *Curr Opin Microbiol.* 2011; 14:392–399. [PubMed: 21803640]
3. Lee HM, Yuk JM, Shin DM, Jo EK. Dectin-1 is inducible and plays an essential role for mycobacteria-induced innate immune responses in airway epithelial cells. *J Clin Immunol.* 2009; 29:795–805. [PubMed: 19633936]
4. Taylor PR, Tsoni SV, Willment JA, Dennehy KM, Rosas M, Findon H, et al. Dectin-1 is required for beta-glucan recognition and control of fungal infection. *Nat Immunol.* 2007; 8:31–38. [PubMed: 17159984]
5. Saijo S, Fujikado N, Furuta T, Chung SH, Kotaki H, Seki K, et al. Dectin-1 is required for host defense against *Pneumocystis carinii* but not against *Candida albicans*. *Nat Immunol.* 2007; 8:39–46. [PubMed: 17159982]
6. Gales A, Conduche A, Bernad J, Lefevre L, Olganier D, Beraud M, et al. PPARgamma controls dectin-1 expression required for host antifungal defense against *Candida albicans*. *PLoS Pathog.* 2010; 6:e1000714. [PubMed: 20062524]
7. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. *N Engl J Med.* 2009; 361:1760–1767. [PubMed: 19864674]
8. Plantinga TS, van der Velden WJ, Ferwerda B, van Spriel AB, Adema G, Feuth T, et al. Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2009; 49:724–732. [PubMed: 19614557]
9. Rosentul DC, Plantinga TS, Oosting M, Scott WK, Velez Edwards DR, Smith PB, et al. Genetic variation in the dectin-1/CARD9 recognition pathway and susceptibility to candidemia. *J Infect Dis.* 2011; 204:1138–1145. [PubMed: 21881131]
10. Plantinga TS, Hamza OJ, Willment JA, Ferwerda B, van de Geer NM, Verweij PE, et al. Genetic variation of innate immune genes in HIV-infected african patients with or without oropharyngeal candidiasis. *J Acquir Immune Defic Syndr.* 2010; 55:87–94. [PubMed: 20577092]
11. Gross O, Gewies A, Finger K, Schafer M, Sparwasser T, Peschel C, et al. Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. *Nature.* 2006; 442:651–656. [PubMed: 16862125]
12. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med.* 2009; 361:1727–1735. [PubMed: 19864672]
13. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol.* 2005; 6:1133–1141. [PubMed: 16200068]

14. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol.* 2005; 6:1123–1132. [PubMed: 16200070]
15. Gaffen SL, Hernandez-Santos N, Peterson AC. IL-17 signaling in host defense against *Candida albicans*. *Immunol Res.* 2011; 50:181–187. [PubMed: 21717069]
16. Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic anti-*Candida albicans* host defense in mice. *J Infect Dis.* 2004; 190:624–631. [PubMed: 15243941]
17. De Luca A, Zelante T, D'Angelo C, Zagarella S, Fallarino F, Spreca A, et al. IL-22 defines a novel immune pathway of antifungal resistance. *Mucosal Immunol.* 2010; 3:361–373. [PubMed: 20445503]
18. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J Exp Med.* 2009; 206:299–311. [PubMed: 19204111]
19. Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against *Candida albicans*. *J Immunol.* 2010; 185:5453–5462. [PubMed: 20921529]
20. Zelante T, De Luca A, Bonifazi P, Montagnoli C, Bozza S, Moretti S, et al. IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance. *Eur J Immunol.* 2007; 37:2695–2706. [PubMed: 17899546]
21. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med.* 2007; 357:1608–1619. [PubMed: 17881745]
22. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature.* 2007; 448:1058–1062. [PubMed: 17676033]
23. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature.* 2008; 452:773–776. [PubMed: 18337720]
24. Conti HR, Baker O, Freeman AF, Jang WS, Holland SM, Li RA, et al. New mechanism of oral immunity to mucosal candidiasis in hyper-IgE syndrome. *Mucosal Immunol.* 2011; 4:448–455. [PubMed: 21346738]
25. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med.* 2011; 208:1635–1648. [PubMed: 21727188]
26. van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LA, Gilissen C, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med.* 2011; 365:54–61. [PubMed: 21714643]
27. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science.* 2011; 332:65–68. [PubMed: 21350122]
28. Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med.* 2010; 207:299–308. [PubMed: 20123959]
29. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med.* 2010; 207:291–297. [PubMed: 20123958]