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IL-22 in antifungal immunity

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Deciphering cellular and molecular mechanisms that maintain host immune homeostasis with fungi and the breakdown of this homeostatic tolerance during fungal infections disease is a challenge in medical mycology. In fact, the virulence of fungi may be determined by the interaction between fungi and the host immune status and its classification as a commensal microorganism or a pathogen may shift depending on the balance. In addition to the central role of the IL-12/IFN-γ-dependent Th1 responses in cell-mediated immune protection against fungi, Th17 cells provide protection and inflammation at mucosal surfaces, and Tregs fine-tune immune responses to prevent damage to the host. Recent evidence indicates that IL-22-producing cells, employing primitive antifungal effector mechanisms, contribute to antifungal resistance at mucosal surfaces under conditions of defective adaptive immunity. The fact that IL-22 production is driven by commensals points to the need of an integrated, systems biology approach to improve our understanding of the inherent and intimate mechanisms underlying multilevel host–fungus interactions.

Keywords: Antifungal immunity · Fungal diseases · IL-22

Introduction

The most serious of the infections caused by fungi are the opportunistic fungal infections that occur in patients with defective immunity, including recipients of solid or hematopoietic stem cell transplant or patients with hematological malignancies. Others include mucosal infections (i.e. thrush, chronic mucocutaneous candidiasis (CMC), recurrent vulvovaginal candidiasis, atopic eczema/dermatitis syndrome), IgE and eosinophilia-driven hypersensitivity diseases, including many cases of severe asthma, allergic bronchopulmonary mycoses, hypersensitivity pneumonitis, gut inflammation and the severe fungal infections occurring in patients with immune reconstitution inflammatory syndrome, an entity characterized by local and systemic inflammatory reactions that can result in quiescent or latent infections manifesting as opportunistic mycoses. The occurrence of fungal diseases in patients with primary immune deficiencies supports the notion that impaired immunity leads to susceptibility to fungal infections and diseases [1, 2].

A fine balance between pro- and anti-inflammatory signals is a prerequisite for a stable host/fungal relationship; the disruption of which may lead to pathological manifestations. This implicates the existence of complex mechanisms of immune adaptations and, of sophisticated mechanisms to antagonize immunity and inflammation– the exploitation of which may contribute to the immune plasticity of the fungal biota [3–5]. In this context, the immunopathogenesis of fungal diseases represents an important paradigm in immunology, which fits within the conceptual framework that modules of immunity have evolved to provide both resistance (i.e. the ability to limit fungal burden), or tolerance (i.e. the ability to limit immune response-associated host damage) [6]. The concept implies that the interaction with the host immune system may determine whether innocuous but opportunistic fungal pathogens maintain "friendly" or "pathogenic" relationships under different settings. In this review, we discuss new findings on the IL-22-dependent pathway, focusing on IL-22's role in the regulation of host-fungus interactions at mucosal surfaces. We highlight recent studies

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linking signals from commensal microbes to the functionality of IL-22-secreting cells.

The interaction of fungi with mammalian hosts: A delicate balance

Studies on non-mammalian hosts have provided means to examine the molecular elements of fungal virulence and host innate immunity [7–9]. In higher organisms however, innate sensing mechanisms are capable of distinguishing between different fungal morphotypes and are equipped to activate distinct adaptive immune responses with protective and non-protective functions against the different fungal species. It has been suggested that a memory-based immune mechanism may have evolved in vertebrates to accommodate colonization by symbiotic microbes while retaining the capacity to oppose their infectivity [10]. This suggests that the adaptive immune system has co-evolved with ubiquitous or commensal fungi, with a price to be paid for this permissiveness.

Stimulation of different antigen presenting cells leads to activation and recruitment of lymphocytes, and the development of distinct types of T helper cell subsets, namely Th1, Th2 and Th17 (Fig. 1). Through cell-bound molecules and secretion of cytokines and other soluble mediators, Th cells may act as immune effectors and, more importantly, as regulators of the appropriate inflammatory and effector responses by immune and

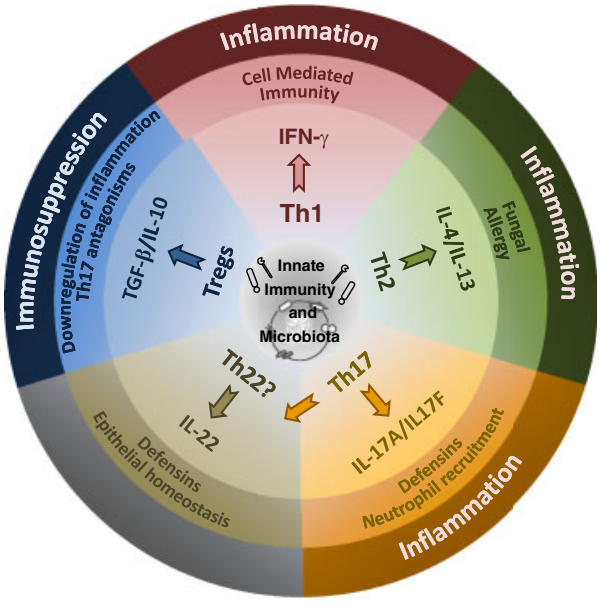

Figure 1. Th cell subsets in fungal infections. The figure shows the orchestration of $CD4^+$ Th and Treg differentiation, their cytokine production and possible functions by innate immune receptors and the intestinal microbiota. Through elaboration of distinct sets of cytokines and other mediators, these cells may act as immune effectors but, more importantly, as master regulators of the inflammatory and barrier activity of innate cells, including epithelial cells that are target of IL-22 (inner circles). The figure also shows the possible consequences of dysregulated Th/Treg immunity (outer circle).

"non-immune" cells of the innate antifungal resistance cascade. Th1 cells are instrumental in the optimal activation of phagocytes at the sites of infection and the development of protective immunity to antifungal vaccines. By dampening protective Th1 responses and promoting the alternative pathway of macrophage activation, Th2 cells may favor fungal infections, allergy and disease relapse; however, Th2-dependent humoral immunity may afford some protection, in part by promoting Th1 immunity and by altering fungal gene expression and intracellular trafficking [11]. Th17 cells appear to have a dichotomous role in antifungal immunity in that they exhibit important effector and regulatory functions in response to fungi at mucosal surfaces, but may also promote pathogenic inflammation (reviewed in [12]).

A side effect of the powerful immune mechanisms of protection against fungi found in higher organisms is inflammation and the associated collateral damage to the host (reviewed in [12]). At this stage, whether "unwanted" immune responses against self, environmental antigens and commensal microorganisms also occur during antifungal immune responses is not well defined, although there is evidence suggesting that fungal sensitization contributes to autoreactivity against self-antigens as a result of shared epitopes with homologous fungal allergens [13]. These side effects may be more devastating than infection itself. Indeed, evidence highlights the dichotomous nature of the inflammatory process during fungal infections. Early inflammation is beneficial, but an uncontrolled inflammatory response may eventually be associated with failure to eradicate the infection and disease progression. An excellent example of this is recent findings in mice with chronic granulomatous disease. In these animals, an intrinsic, genetically determined failure to control inflammation to sterile fungal components determines the animals' inability to resolve infection with *A. fumigatus* [14]. The data have direct implications for the treatment of fungal infections in the clinic: it is likely that the exaggerated inflammatory response compromises the ability of the host to cope with infecting/colonizing fungi, and not an "intrinsic" susceptibility to infection that determines a state of chronic or uncontrolled disease.

A protective immune response to fungi must oppose fungal infectivity and ensure survival, while limiting collateral damage and restoring a homeostatic environment (also referred to as "protective tolerance") [15]. This can be achieved through the ability to control both the type and the magnitude of the immune responses and involves numerous mechanisms, among which Treg-mediated suppression of inflammation associated with infection plays a prominent role. As critical gatekeepers in immune homeostasis, Tregs have become an integral component of the antifungal immune response. Through Tregs' capacity to inhibit innate and adaptive antifungal immunity, Tregs are strictly required for the generation of protective tolerance; however, as Tregs dampen the efficacy of protective immunity, fungal persistence may be a consequence of Treg activity (Fig. 1). It is not surprising that fungi have evolved mechanisms to hijack or manipulate the regulatory network of the host, thereby operating by stealth to generate conditions that secure their survival

by limiting the immune response (also as a consequence, reduced damage to the host) [16, 17]. In doing so, similar to symbionts, the commensal yeasts have been shown to contribute to the balance of inflammation and tolerance at mucosal surfaces and at distant sites to the benefit of the mammalian host [18].

IL-22-producing cells

Epithelial cells are a central component of the mucosal immune system of the gut and the lung. The release of epithelial cytokines and chemokines are important events in initiating mucosal inflammatory responses. Epithelial cells express receptors for microbial-associated molecular patterns and thus respond to signals delivered by the microbiota. These receptors activate signaling pathways that finely modulate epithelial cell production of antimicrobial products and chemokines. IL-22, a member of the IL-10 cytokine family, is one such dedicated signal –it plays a crucial role in the innate immune defense and mucosal protection from damage. Produced by Th22, Th1, Th17, NK22 (identified by CD127, CD56 and NKp44 expression in humans [19]), NKT, $\gamma\delta^+$ T cells and lymphoid tissue-inducer cells [20], IL-22 regulates intestinal and skin homeostasis and mucosal wound healing via activation of the JAK/STAT pathway, which results in tyrosine phosphorylation of epithelial STAT3 [20, 21]. IL-22 receptor expression is restricted to the tissues and not on cells of the innate immune system, providing a way by which the immune system exerts control over tissue homeostasis.

Another cytokine that is crucial in the antifungal immune cascade is IL-23. It is known that IL-23 can increase the pathogenic potential of Th17 cells in vivo, but IL-23 can also operate independently of Th17. The finding that IL-23 exhibited antifungal protection in condition of IFN-γ deficiency [22] suggests that IL-23 may operate beyond the production of IL-17A/IL-17F. It has recently been described that IL-23 is crucial for the production of IL-22, which provides protective antibacterial immunity in the absence of IL-12 [20]. Through the exploitation of primitive antifungal defense mechanisms, IL-22 is crucially involved in the control of *Candida* growth at mucosal sites in conditions of Th1 and Th17 deficiency [23]. Thus, by expanding Th17 effector cells [22] and IL-22-producing cells [23], IL-23 has a dual role in infection.

As mentioned, IL-22 can be produced by gut DC, $NKp46^+$ (referred to as NCR22 in mice, [24]) and $CD4^+$ T cells, and directly targets gut epithelial cells to induce STAT3 phosphorylation and the release of S100A8 and S100A9 peptides, which are endowed with antifungal and anti-inflammatory effects [23]. Thus, due to dominant-negative mutations of STAT3, patients with autosomal dominant hyper-IgE syndrome (AD-HIES) have a defective Th17 response [25], which is likely to be amplified on epithelial cells where STAT3 mutation compromises the effects of IL-22. Vaginal epithelial cells also produced S100A8 and S100A9 following interaction with *Candida* [26], suggesting the possible involvement of IL-22 in vaginal candidiasis. Not only are naturally occurring $IL\text{-}22^+$ cells highly enriched at mucosal sites, where continuous exposure to fungi occurs, but also memory *C. albicans*-specific $IL\text{-}22^+CD4^+$ cells are present in the human T-cell repertoire [27] and are defective in patients with CMC [28–30]. Autoantibodies against IL-22, in addition to IL-17A and IL-17F, were observed in patients with CMC and considered to be associated with susceptibility to CMC [31, 32]. We detected high levels of autoantibodies to IL-22 in nearly all, and autoantibodies to IL-17A and IL-17F in 20% of the sera from APS-1 patients with CMC [33]. Thus, it is likely that inhibition of IL-22 may dampen antifungal resistance in these patients, eventually leading to enhanced IL-17A secretion as a consequence of chronic stimulation caused by defective yeast clearance. In fact, Th17 responses are either decreased, along with Th1 responses [25, 29], or increased in patients with CMC [29, 33]. Thus, although autoantibodies to IL-22 and/or IL-17 is correlated with susceptibility to CMC, this correlation could be either the primary cause of candidiasis or a consequence of an enhanced Th17 response. It has been shown that autoantibodies to pro-inflammatory cytokines may be considered as "beneficial" autoimmunity in their ability to dampen pro-inflammatory mediators and restrict self-destructive immunity [34]. Therefore, a direct connection between anti-cytokine antibodies, inhibition of antifungal immunity and susceptibility to CMC remains to be demonstrated.

The new findings suggest that $IL\text{-}22^+$ cells, employing primitive antifungal effector mechanisms, contribute to antifungal resistance at mucosal surfaces under conditions of defective adaptive immunity. The findings also support a model in which the IL-23/IL-22 axis controls the initial fungal growth and tissue homeostasis, while adaptive Th1/Treg prevent fungal dissemination and provide memory and tolerance [6]. The two pathways are non-redundant, reciprocally regulated and compensate for each other in the relative absence of one another, consistent with the theme that adaptive immunity depends on innate immunity but innate immunity also requires adaptive regulation. In the presence of a functional Th1 pathway, the IL-23/IL-22 axis is dispensable, and this may account for the mild susceptibility to candidiasis seen in otherwise immunocompetent IL-22-deficient mice [23, 35, 36]. However, in condition of defective Th1 pathway, an innate IL-22-driven response accounts for resistance to low-infective fungal exposure. While IL-22 can be produced by Th17 cells and shares activities with members of the IL-17 family, IL-22 may also work independently of Th17 cells, as shown by the ability of IL-22 to compensate for IL-17RA deficiency in mice with mucosal candidiasis [23]. It is of interest in this regard that the IL-22 pathway is exploited by non-pathogenic yeasts, such as *C. krusei* and *Saccharomyces cerevisiae* [23] and also *Cryptococcus neoformans*, against which a protective effect of IL-23 has been demonstrated [37]. Considering the burden of nosocomial infections by opportunistic yeast species, the new finding may offer new interpretative clues to explain why some individuals are at high risk of yeast infections. Table 1 reports the available findings supporting a role for IL-22 in antifungal defense at mucosal surfaces.

Table 1. A summary of the role of IL-22 in antifungal host defense at mucosal surfaces

Role of IL-22	Reference
IL-22 contributes to antifungal resistance at mucosal surfaces under conditions of defective Th-adaptive immunity. The two pathways are non-redundant, reciprocally regulated and compensate each other in the relative absence of either one	[23]
In the presence of a functional Th1 pathway, IL-22 is dispensable, and this may account for the mild susceptibility to cutaneous or oropharyngeal candidiasis seen in otherwise immunocompetent IL-22-deficient mice	[23, 35, 36]
Although produced by Th17 cells and sharing activities with members of the IL-17 family, IL-22 compensates for IL-17A deficiency in mice with mucosal candidiasis	[23]
Blockade of IL-22 exacerbates pulmonary aspergillosis in mice	(Our unpublished observations)
Distinct levels of IL-22 correlate with pattern of susceptibility and resistance to vaginal candidiasis in mice	(Our unpublished observations)

Microbiota–immune system–fungi interaction: A ménage à trois

As mentioned, IL-22 production can occur in the relative absence of Th17 cells [23], a finding clearly pointing to mechanisms of IL-22 production outside of the Th17 pathway. The microbiota impacts host nutrition, protection and tissue development. Alterations in microbiota composition are associated with susceptibility to various infections and both local and systemic pathological immune responses [38]. Early alterations of airway microbiota in infants have been correlated with development of respiratory allergy later in life [39]. The fact that IL-22 production in the gut is driven by commensals may provide novel mechanistic insights on how intestinal dysbiosis following antibiotic therapy, radiation or metabolic inflammation, predisposes individuals to candidiasis and, more generally, how bacterial–fungal population dynamics impacts homeostasis and inflammatory diseases at mucosal surfaces. The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that mediates IL-22 production [40]. A variety of indole derivatives act as endogenous ligands for AhR [41] and are generated through conversion from dietary tryptophan by commensal intestinal microbes [42, 43]. Thus, the tryptophan metabolism pathway is likely exploited by commensals and the mammalian host to increase immunological fitness in response to fungi.

Concluding remarks

The discovery of Th17 cells and IL-22 in the field of fungal immunology has offered new grounds for a better comprehension of the basic mechanisms underlying the balance between resistance and tolerance to ubiquitous or commensal fungi and the consequence of its imbalance that may result in unfavorable host–fungus associations. Future studies are needed to better position the activity of IL-22 within the Th17-dependent antifungal immunity in response to fungi at different sites within the host. Ultimately, defining the "friendly" versus the "pathogenic" signature of fungi at the multifaceted interface with the mammalian host will define how immune dysregulation may lead to progressive fungal infections and/or how the fungal biota impacts the burst and perpetration of pathogenic inflammation and, possibly, autoimmunity in the modern era [44].

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References

1 **Romani, L.,** Cell mediated immunity to fungi: a reassessment. *Med. Mycol.* 2008. **46**: 515–529.

2 **Carneiro-Sampaio, M. and Coutinho, A.,** Immunity to microbes: lessons from primary immunodeficiencies. *Infect. Immun.* 2007. **75**: 1545–1555.

3 **Romani, L.,** Immunity to fungal infections. *Nat. Rev. Immunol.* 2004. **4**: 1–23.

4 **Brown, G. D.,** How fungi have shaped our understanding of mammalian immunology. *Cell Host Microbe* 2010. **7**: 9–11.

5 **Levitz, S. M.,** Innate recognition of fungal cell walls. *PLoS Pathog.* 2010. **6**: e1000758.

6 **Zelante, T., De Luca, A., D'Angelo, C., Moretti, S. and Romani, L.,** IL-17/Th17 in anti-fungal immunity: what's new? *Eur. J. Immunol.* 2009. **39**: 645–648.

7 **Fuchs, B. B. and Mylonakis, E.,** Using non-mammalian hosts to study fungal virulence and host defense. *Curr. Opin. Microbiol.* 2006. **9**: 346–351.

8 **Mylonakis, E., Casadevall, A. and Ausubel, F. M.,** Exploiting amoeboid and non-vertebrate animal model systems to study the virulence of human pathogenic fungi. *PLoS Pathog.* 2007. **3**: e101.

9 **Peleg, A. Y., Tampakakis, E., Fuchs, B. B., Eliopoulos, G. M., MoelleringJr, R. C. and Mylonakis, E.,** Prokaryote-eukaryote interactions identified by using *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA* 2008. **105**: 14585–14590.

10 **McFall-Ngai, M. J.,** Care for the community: a memory-based immune system may have evolved in vertebrates because of the need to recognize and manage complex communities of beneficial microbes. *Nature* 2007. **445**: 153.

11 **McClelland, E. E., Nicola, A. M., Prados-Rosales, R. and Casadevall, A.,** Ab binding alters gene expression in *Cryptococcus neoformans* and directly modulates fungal metabolism. *J. Clin. Invest.* 2010. **120**: 1355–1361.

12 **Romani, L.,** Immunity to fungal infections. *Nat. Rev. Immunol.* 2011. In press

13 **Zeller, S., Glaser, A. G., Vilhelmsson, M., Rhyner, C. and Crameri, R.,** Immunoglobulin-E-mediated reactivity to self antigens: a controversial issue. *Int. Arch. Allergy Immunol.* 2008. **145**: 87–93.

14 **Romani, L., Fallarino, F., De Luca, A., Montagnoli, C., D'Angelo, C., Zelante, T., Vacca, C. et al.,** Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease. *Nature* 2008. **451**: 211–215.

15 **Romani, L. and Puccetti, P.,** Protective tolerance to fungi: the role of IL-10 and tryptophan catabolism. *Trends Microbiol.* 2006. **14**: 183–189.

16 **Rappleye, C. A. and Goldman, W. E.,** Fungal stealth technology. *Trends Immunol.* 2008. **29**: 18–24.

17 **Aimanianda, V., Bayry, J., Bozza, S., Kniemeyer, O., Perruccio, K., Elluru, S. R., Clavaud, C. et al.,** Surface hydrophobin prevents immune recognition of airborne fungal spores. *Nature* 2009. **460**: 1117–1121.

18 **Noverr, M. C. and Huffnagle, G. B.,** Does the microbiota regulate immune responses outside the gut? *Trends Microbiol.* 2004. **12**: 562–568.

19 **Cella, M., Fuchs, A., Vermi, W., Facchetti, F., Otero, K., Lennerz, J. K., Doherty, J. M. et al.,** A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* 2009. **457**: 722–725.

20 **Witte, E., Witte, K., Warszawska, K., Sabat, R. and Wolk, K.,** Interleukin-22: a cytokine produced by T, NK and NKT cell subsets, with importance in the innate immune defense and tissue protection. *Cytokine Growth Factor Rev.* 2010. **21**: 365–379.

21 **Pickert, G., Neufert, C., Leppkes, M., Zheng, Y., Wittkopf, N., Warntjen, M., Lehr, H. A. et al.,** STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. *J. Exp. Med.* 2009. **206**: 1465–1472.

22 **Zelante, T., De Luca, A., Bonifazi, P., Montagnoli, C., Bozza, S., Moretti, S., Belladonna, M. L. et al.,** IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance. *Eur. J. Immunol.* 2007. **37**: 2695–2706.

23 **De Luca, A., Zelante, T., D'Angelo, C., Zagarella, S., Fallarino, F., Spreca, A., Iannitti, R. G. et al.,** IL-22 defines a novel immune pathway of antifungal resistance. *Mucosal Immunol.* 2010. **3**: 361–373.

24 **Satoh-Takayama, N., Lesjean-Pottier, S., Vieira, P., Sawa, S., Eberl, G., Vosshenrich, C. A. and Di Santo, J. P.,** IL-7 and IL-15 independently program the differentiation of intestinal CD3-NKp46+cell subsets from Id2-dependent precursors. *J. Exp. Med.* 2010. **207**: 273–280.

25 **Milner, J. D., Brenchley, J. M., Laurence, A., Freeman, A. F., Hill, B. J., Elias, K. M., Kanno, Y. et al.,** Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature* 2008. **452**: 773–776.

26 **Yano, J., Lilly, E., Barousse, M. and FidelJr, P. L.,** Epithelial cell-derived S100 calcium-binding proteins as key mediators in the hallmark acute neutrophil response during *Candida* vaginitis. *Infect. Immun.* 2010. **78**: 5126–5137.

27 **Liu, Y., Yang, B., Zhou, M., Li, L., Zhou, H., Zhang, J., Chen, H. and Wu, C.,** Memory IL-22-producing CD4+T cells specific for *Candida albicans* are present in humans. *Eur. J. Immunol.* 2009. **39**: 1472–1479.

28 **Eyerich, K., Eyerich, S., Hiller, J., Behrendt, H. and Traidl-Hoffmann, C.,** Chronic mucocutaneous candidiasis, from bench to bedside. *Eur. J. Dermatol.* 2010. **20**: 260–265.

29 **Ng, W. F., von Delwig, A., Carmichael, A. J., Arkwright, P. D., Abinun, M., Cant, A. J., Jolles, S. and Lilic, D.,** Impaired T(H)17 responses in patients with chronic mucocutaneous candidiasis with and without autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J. Allergy Clin. Immunol.* 2010. **126**: 1006–1015.

30 **van der Meer, J. W., van de Veerdonk, F. L., Joosten, L. A., Kullberg, B. J. and Netea, M. G.,** Severe *Candida* spp. infections: new insights into natural immunity. *Int. J. Antimicrob. Agents* 2010. **36**: S58–S62.

31 **Kisand, K., Boe Wolff, A. S., Podkrajsek, K. T., Tserel, L., Link, M., Kisand, K. V., Ersvaer, E. et al.,** Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J. Exp. Med.* 2010. **207**: 299–308.

32 **Puel, A., Doffinger, R., Natividad, A., Chrabieh, M., Barcenas-Morales, G., Picard, C., Cobat, A. 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.

33 **Ahlgren, K. M., Moretti, S., Ardesjö Lundgren, B., Karlsson, I., Åhlin, E., Norling, A., Hallgren, Å. et al.,** Increased IL-17A secretion in response to *Candida albicans* in autoimmune polyendocrine syndrome type 1 and its animal model. *Eur. J. Immunol.* 2011. **41**: 235–245.

34 **Wildbaum, G., Nahir, M. A. and Karin, N.,** Beneficial autoimmunity to proinflammatory mediators restrains the consequences of self-destructive immunity. *Immunity* 2003. **19**: 679–688.

35 **Kagami, S., Rizzo, H. L., Kurtz, S. E., Miller, L. S. and 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.

36 **Conti, H. R., Shen, F., Nayyar, N., Stocum, E., Sun, J. N., Lindemann, M. J., Ho, A. W. 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.

37 **Kleinschek, M. A., Muller, U., Brodie, S. J., Stenzel, W., Kohler, G., Blumenschein, W. M., Straubinger, R. K. et al.,** IL-23 enhances the inflammatory cell response in *Cryptococcus neoformans* infection and induces a cytokine pattern distinct from IL-12. *J. Immunol.* 2006. **176**: 1098–1106.

38 **Cerf-Bensussan, N. and Gaboriau-Routhiau, V.,** The immune system and the gut microbiota: friends or foes? *Nat. Rev. Immunol.* 2010. **10**: 735–744.

39 **Bisgaard, H., Hermansen, M. N., Buchvald, F., Loland, L., Halkjaer, L. B., Bonnelykke, K., Brasholt, M. et al.,** Childhood asthma after bacterial colonization of the airway in neonates. *N. Engl. J. Med.* 2007. **357**: 1487–1495.

40 **Trifari, S., Kaplan, C. D., Tran, E. H., Crellin, N. K. and Spits, H.,** Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. *Nat. Immunol.* 2009. **10**: 864–871.

41 **Heath-Pagliuso, S., Rogers, W. J., Tullis, K., Seidel, S. D., Cenijn, P. H., Brouwer, A. and Denison, M. S.,** Activation of the Ah receptor by tryptophan and tryptophan metabolites. *Biochemistry* 1998. **37**: 11508–11515.

42 **Bjeldanes, L. F., Kim, J. Y., Grose, K. R., Bartholomew, J. C. and Bradfield, C. A.,** Aromatic hydrocarbon responsiveness-receptor agonists generated from indole-3-carbinol in vitro and in vivo: comparisons with 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Proc. Natl. Acad. Sci. USA* 1991. **88**: 9543–9547.

43 **Cheng, S. C., van de Veerdonk, F., Smeekens, S., Joosten, L. A., van der Meer, J. W., Kullberg, B. J. and Netea, M. G.,** *Candida albicans* dampens host defense by downregulating IL-17 production. *J. Immunol.* 2010. **185**: 2450–2457.

44 **Romani, L.,** Parasites and autoimmunity: the case of fungi. *Autoimmun. Rev.* 2008. **8**: 129–133.

Abbreviation: **CMC:** chronic mucocutaneous candidiasis

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