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Cutting Edge: IL-17–Secreting Innate Lymphoid Cells Are Essential for Host Defense against Fungal Infection

André Gladiator, Nicolette Wangler, Kerstin Trautwein-Weidner, and Salomé LeibundGut-Landmann

IL-17–mediated immunity has emerged as a crucial host defense mechanism against fungal infections. Although Th cells are generally thought to act as the major source of IL-17 in response to *Candida albicans*, we show that fungal control is mediated by IL-17–secreting innate lymphoid cells (ILCs) and not by Th17 cells. By using a mouse model of oropharyngeal candidiasis we found that IL-17A and IL-17F, which are both crucial for pathogen clearance, are produced promptly upon infection in an IL-23–dependent manner, and that ILCs in the oral mucosa are the main source for these cytokines. Ab-mediated depletion of ILCs in RAG1-deficient mice or ILC deficiency in retinoic acid–related orphan receptor (ROR)γt−/− mice resulted in a complete failure to control the infection. Taken together, our data uncover the cellular basis for the IL-23/IL-17 axis, which acts right at the onset of infection when it is most needed for fungal control and host protection. *The Journal of Immunology*, 2013, 190: 521–525.

Fungal infections exhibit a serious health hazard, in particular in immunocompromised patients. *Candida albicans*, one of the clinically most relevant fungal pathogens, can cause superficial infections of the skin, the oral or the vaginal mucosa, or it can disseminate systemically and thereby account for significant morbidity and mortality. IL-17–mediated immunity has emerged as a crucial host defense mechanism against fungal infections (1, 2). Allelic variations in genes of the IL-17 pathway have recently been linked with fungal diseases, in particular chronic mucocutaneous candidiasis (3). IL-17 also plays a central role for protective antifungal immunity in mice. Defects in IL-17 production or function render mice unable to control mucosal and cutaneous infections or systemic dissemination of *C. albicans* (4–6). Th cells are widely accepted as crucial players of protective antifungal immunity and are seen as the principal source of IL-17 during fungal infections (7). Indeed, fungi drive the differentiation of T cells into Th17 cells (8, 9), and *C. albicans*–specific T cells present in the peripheral blood of healthy individuals belong preferentially to this subset (10).

The failure of IL-17RA−/− mice to control *C. albicans* is apparent from the first days of infection (4). The immediate requirement of IL-17, however, is inconsistent with an involvement of Th17 cells, given the time these cells need to differentiate into cytokine-secreting effector cells. This raises the question about alternative cellular sources of IL-17, which could provide this important immune mediator when it is most needed right after fungal encounter by the host. Subsets of γδ T cells, NK cells, and innate lymphoid cells (ILCs) producing IL-17 have recently been identified in the skin and at mucosal surfaces where they act as an important first line of defense (11). The subset of retinoic acid–related orphan receptor (ROR)γt−expressing ILCs secretes IL-17 and/or IL-22 and promotes immunity or inflammation. They can mediate protective immunity against infectious agents (12, 13) and function in homeostasis and tissue repair (14, 15), but they have also been shown to exert pathogenic potential in certain situations (16, 17). However, ILCs have never been linked to immunity against fungal pathogens. In this study we show that ILCs are the major source of IL-17 in response to *C. albicans* and that, unlike T cells, they are essential and sufficient for IL-17–mediated protective immunity against the fungus in the oral mucosa.

**Materials and Methods**

**Mice**

C57BL/6 mice were purchased from Janvier Elevage, and *rage−/−*, *rag1−/−*, *mhcII−/−*, *p19−/−*, *TCRβ−/−*, and *Jα18−/−* mice were bred at the Institute of Laboratory Animal Sciences (University of Zurich, Zurich, Switzerland); *il17−/−*, *il22−/−*, and *cd1d−/−* mice were bred at our animal facility Rodent Center HCI. All mice were on the C57BL/6 background and were used at 6–15 wk age. All mouse experiments were conducted in accordance with the guidelines of the Swiss Animal Protection Law and were approved by the Institute of Microbiology, Swiss Federal Institute of Technology Zürich, 8093 Zurich, Switzerland

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A.G. and S.L.-L. designed the experiments; A.G., N.W., and K.T.-W. performed the experiments; A.G., N.W., K.T.-W., and S.L.-L. analyzed the data; and A.G. and S.L.-L. wrote the manuscript.

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Abbreviations used in this article: ILC, innate lymphoid cell; OPC, oropharyngeal candidiasis; PAS, periodic-acid Schiff; ROR, retinoic acid–related orphan receptor.

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Fungal strain and infection

The C. albicans laboratory strain SC5314 was grown in yeast extract/peptone/glucose medium at 30°C for 15–18 h. Mice were infected with 2.5 × 10^6 CFU C. albicans sublingually as described (4) without immunosuppression. In some experiments, anti–IL-17A (BioXCell, clone 17F3, 200 μg/mouse/d) and anti–IL-17F (provided by Pfizer Biotherapeutics, 200 μg/mouse/d) or anti–CD90.2 (BioXCell, clone 30H12, 200 μg/mouse every second day) was administered starting from 1 d prior to infection via the i.p. route. Mice were monitored for morbidity and euthanized when they showed severe signs of pain or distress. Loss and recovery of body weight was monitored throughout the course of all experiments. For determination of fungal burden the tongue was homogenized in sterile 0.05% Nonidet P-40 in H_2O and serial dilutions were plated on yeast extract/peptone/dextrose agar containing 100 μg/ml ampicillin.

Isolation and stimulation of cells, flow cytometry

Mice were anesthetized with a subcutaneous dose of ketamine, xylazine, and acepromazine and perfused by injection of PBS into the right heart ventricle. Tongues were cut into fine pieces and digested with DNase I (Roche, 2.4 mg/ml) and collagenase IV (Invitrogen, 4.8 mg/ml) in PBS for 45 min at 37°C. Single-cell suspensions were subjected to a discontinuous Percoll (Sigma-Aldrich) gradient and lymphocytes were collected from the 70/40% interphase. Cells were then stained, and data were acquired on a LSRII (BD Biosciences) and analyzed with FlowJo software (Tree Star).

RNA isolation and real-time RT-PCR

Isolation of total RNA from tongues and generation of cDNA were carried out according to standard protocols. Quantitative PCR was performed using SYBR Green (Roche) and a Rotor-Gene 3000 (Corbett Life Science). The primers used were: IL-17A, forward, 5'-GCTCCAGAGCGCTCAGA-3', reverse, 5'-AGCTTTCCTCCGATTGA-3'; IL-17F, forward, 5'-GAGGATAACTGGCTGTCT-3', reverse, 5'-GAGTTCATGTTCTGTTC-3'. Data were normalized to β-actin and are displayed as fold induction relative to naive.

Histology

Tissues were embedded in OCT (Sakura Finetek) and snap-frozen in liquid nitrogen. Sagittal cryosections (10 μm) were prepared and stained with hematoxylin for visualization of C. albicans of the tongue of the indicated mice were stained with PAS and counterstained with hematoxylin (Carl Roth). Sections were mounted with Pertex (Biosystems Switzerland) and analyzed on an Axiovert 25 (Zeiss) at ×10–40 magnification.

Statistics

Statistical significance was determined by a nonparametric Mann–Whitney U test using GraphPad Prism (GraphPad Software) with *p < 0.05, **p < 0.01, and ***p < 0.001.

Results and Discussion

The adaptive immune system is dispensable for the resolution of oropharyngeal C. albicans infection

During oropharyngeal candidiasis (OPC), fungus-specific Th cells differentiate selectively into IL-17–producing effector cells (8). To evaluate the protective capacity of Th17 cells during OPC, we analyzed MHC class II^−/− mice for their capability to control C. albicans in the oral mucosa. To our surprise, these animals showed normal weight recovery post-infection and cleared C. albicans as efficiently as did wild-type controls (Fig. 1A, 1B). Even RAG1^−/− mice, which are completely devoid of T and B cells, controlled the infection with only a slight delay (Fig. 1A, 1B). This also held true during secondary infection where MHC class II^−/− and RAG1^−/− mice did again not display any defect in fungal clearance compared with wild-type mice, in which C. albicans–specific Th cells had been primed (data not shown). Histological analysis of the tongue tissue from infected mice confirmed that MHC class II^−/− and RAG1^−/− mice recovered fully from OPC (Fig. 1C). These findings reveal that the adaptive immune system is dispensable for antifungal immunity in the oral mucosa. In contrast, the neutralization of IL-17A and IL-17F during the course of OPC caused severe disease associated with defective weight recovery and fungal clearance (Fig. 1D, 1E). IL-17A and IL-17F seemed to have redundant and/or compensating effects (18) and were both required for optimal protection from OPC, although IL-17A appeared to be more important (Supplemental Fig. 1). The essential role of IL-17A and IL-17F for antifungal host defense in absence of adaptive immunity implies that T cells are not the source of these cytokines, at least during the early phase of OPC.

ILCs are the primary source of IL-17 during OPC

To identify the cellular source of IL-17A and IL-17F during OPC, we measured the mRNA of these cytokines in the tongue

![Figure 1](http://www.jimmunol.org/)
of infected animals. The expression of both cytokines was detectable at high levels from 24 h postinfection and remained high up to at least 72 h postinfection (Fig. 2A) (19). In line with our previous finding that Th cells did not contribute to IL-17–mediated immunity in response to C. albicans, MHC class II–deficient animals expressed normal levels of IL-17A and IL-17F mRNA (Fig. 2B). The same was also true for mice lacking γδ T cells (TCRδ−/−) or NKT cells (CD1d−/− and Ja18−/−) (Fig. 2C, 2D and data not shown), indicating that these innate T cell populations do not contribute significantly to IL-17 immunity in the oral mucosa, although they can act as a source of IL-17 in other tissues (20–22).

Prominent RAG-independent cells producing IL-17 are ILCs, and they have even been reported to do so in response to yeast cell wall products (23). When analyzing the cellular composition of the tongue of RAG1−/− mice we detected a population of ILCs as defined by their CD45+ lineage−CD90+Sca-1+CD127+ phenotype (Fig. 2E, 2F). To confirm that ILCs are required for IL-17 production, we depleted CD90+ cells in Rag1−/− mice and thereby strongly reduced IL-17A and IL-17F mRNA induction upon OPC (Fig. 2F and data not shown). Moreover, that lack ILCs owing to a targeted deletion of RORγt displayed a similar reduction of cytokine mRNA expression (Fig. 2G and data not shown). This further supported a crucial role of these cells as major producers of IL-17 in response to C. albicans in the oral mucosa.

ILCs are key players in mediating host defense against C. albicans

We next addressed the question of whether ILCs had any protective role during OPC. Depletion of CD90+ cells in RAG1−/− mice did indeed prevent the animals to control the infection. They did not regain their initial body weight (Fig. 3A) and maintained a high fungal burden in the tongue (Fig. 3B). Moreover, infection-induced lesions of the epithelial barrier and the subepithelial tissue did not heal up to day 7 postinfection (Fig. 3C). In line with this, RORC−/− mice also failed to clear the fungus and to recover from infection (Fig. 3D, 3E). Taken together, these data make a strong case for IL-17–producing ILCs acting as the main regulators of IL-17–mediated immunity for fungal clearance and host protection during OPC.

It has previously been reported that IL-17 production by ILCs is regulated by IL-23 (16). We found that this was also true during OPC where IL-17 induction in the tongue was completely abolished in the absence of IL-23 (Fig. 3F and data not shown). The lack of IL-17 induction in IL-23−deficient mice translated into a complete failure of these mice to control the infection (Fig. 3D, 3E). In contrast, IL-1R and IL-6 were not required for ILC-derived IL-17 production and for fungal clearance (Fig. 3G, 3H and data not shown). Although the requirement of IL-23 for optimal antifungal defense has been observed previously (4), the strong susceptibility of IL-23−deficient mice has always been attributed to a defect in Th17 cells despite the fact that the inability of these mice to control the infection is evident before effector T cells have fully differentiated (4). Our data now explain how IL-23 acts right at the onset of infection, well aligned with the kinetics of the infection process and its resolution. Other factors that have been linked to antifungal defense, including those found mutated in rare cases of chronic mucocutaneous candidiasis, may exert their impact on IL-17 immunity by regulating ILCs rather than (or in addition to) Th cells. Future investigations will be needed to establish whether a defect in IL-17–secreting ILCs predisposes to fungal infections in humans. This hypothesis is supported by the recent finding that SIV infection of macaques, a situation similar to HIV infection in humans, which predisposes to OPC, resulted in a significant loss of IL-17+ ILCs (24).

ILCs have diverse functions ranging from lymph node development to the induction of autoimmunity. Whereas the

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**FIGURE 2.** ILCs are the essential source of IL-17 during OPC. (A) Mice were infected sublingually with C. albicans and RNA was isolated from the tongue at the indicated time points. IL-17A and IL-17F mRNA expression was analyzed in duplicates by real-time RT-PCR. Data are pooled from two independent experiments (n = 4 for each time point, except at 16 h, where n = 2). (B) IL-17A and IL-17F mRNA expression in the tongue of MHC class II−/− (n = 5) and wild-type control mice (n = 5) at 24 h postinfection. (C and D) IL-17A mRNA expression in the tongue of CD1d−/− (n = 5; C) and TCRδ−/− mice (n = 3; D) compared with wild-type controls (n = 5 each) at 24 h postinfection. (E) ILCs in the tongue of infected Rag1−/− mice were identified as CD45.2+ (not shown), lineage− (CD3−, CD5−, Gr−1−, CD11b−, B220−), CD90.2+, Sca1+, and CD127+. Gray histograms show isotype controls; solid line shows Sca-1 or CD127 staining. (F) IL-17A mRNA expression in the tongue of Rag1−/− (n = 6), IL-17A−/− and IL-17F−/−depleted Rag1−/− (n = 6), and wild-type control animals (n = 6) at 24 h postinfection. (G) IL-17A mRNA expression in the tongue of Rorc−/− (n = 6) and wild-type control animals (n = 4). Data in (B)–(D), (F), and (G) are pooled from two independent experiments. Data in (D) are representative of three independent experiments. *p < 0.05.
emphasize the key role of the IL-23/IL-17 axis during fungal infections and reveal a new cellular basis for IL-17–mediated antifungal immunity. Instead of Th17 cells, IL-17–producing ILCs take center stage when immediate defense in the oral mucosa is most needed to confine the invading pathogens and protect the host.

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Disclosures
The authors have no financial conflicts of interest.

References
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FIGURE 3. ILCs are key players in mediating host defense against C. albicans. (A) RAG1−/− (n = 5), CD90.2-depleted RAG1−/− (n = 5), and wild-type control animals (n = 5) were infected sublingually with C. albicans and weighed daily. Note that RAG1−/− and wild-type animals are from the same experiment as the ones shown in Fig. 1D. (B) Fungal burden in the tongue of RAG1−/− (n = 9), CD90.2-depleted RAG1−/− (n = 8), and wild-type control animals (n = 6) were analyzed on day 7 postinfection. Each symbol represents one mouse. Data are pooled from two independent experiments. (C) Sagittal sections of the tongue of infected RAG1−/− and CD90.2-depleted RAG1−/− mice on day 7 postinfection were stained with PAS and counterstained with hematoxylin for visualization of C. albicans and the cell nuclei. Sections shown are representative of three separate mice. Scale bars, 100 μm. (D) RORC+ mice (n = 4), IL-23p19−/− (n = 7), and wild-type control animals (n = 4) were infected sublingually with C. albicans and weighed daily. (E) Fungal burden in the tongue of the mice shown in (D) were analyzed on day 7 postinfection. Each symbol represents one mouse. (F-H) IL-17A mRNA expression in the tongue of IL-23p19−/− mice (n = 6; F), IL-1R−/− mice (n = 5; G), and IL-6−/− mice (n = 6; H) compared with wild-type controls (n = 3 each) at 24 h postinfection. All data are representative of two to four independent experiments. *p < 0.05, **p < 0.01, ***p < 0.001.

IL-22–producing subset of ILCs is thought to mediate homeostasis and antimicrobial defense at mucosal surfaces (25, 26), its IL-17–secreting counterpart has a strong pathologic potential (16). To our knowledge, in this study we show for the first time that IL-17+ ILCs are highly beneficial to the host and act as a first line of defense. In conclusion, our data

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Fig. S1. IL-17A and IL-17F act synergistically. (A) IL-17A+/- and IL-17A-/- mice were infected sublingually with C. albicans and the fungal burden in the tongue was analyzed on day 3 and day 5 post-infection. (B) WT mice were treated with neutralizing antibodies specific for IL-17A and/or IL-17F before they were infected sublingually with C. albicans. The fungal burden in the tongue was analyzed on day 5 post-infection. Each symbol represents one mouse.