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*Published online 6 April 2015*

http://www.jimmunol.org/content/early/2015/04/04/jimmunol.1402986

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IL-33 Enhances Host Tolerance to Candida albicans Kidney Infections through Induction of IL-13 Production by CD4⁺ T Cells

Vuvi G. Tran,* Hye J. Kim,† Juyang Kim,† Sang W. Kang,* U J. Moon,* Hong R. Cho,†‡ and Byungsuk Kwon*

Susceptibility to systemic Candida albicans infection is determined by immune resistance, as well as by the ability to control Candida-induced immunopathologies. We showed previously that exogenous IL-33 can increase resistance to peritoneal C. albicans infection by regulating multiple steps of the neutrophil anti-Candida response. In this study, using a mouse model of systemic candidiasis, we observed that IL-33 administration limited fungal burden and inflammation and increased survival. In kidneys, IL-33 seemed to directly act on neutrophils and CD4⁺ T cells: IL-33 administration enhanced fungal clearance by increasing neutrophil phagocytic activity without which Candida proliferation was uncontrollable. In contrast, IL-33 stimulated CD4⁺ T cells to produce IL-13, which, in turn, drove the polarization of macrophages toward the M2 type. Furthermore, the absence of IL-13 abolished IL-33-mediated polarization of M2 macrophages and renal functional recovery. In addition, IL-33 and IL-13 acted synergistically to increase M2 macrophage polarization and its phagocytic activity. Overall, this study identifies IL-33 as a cytokine that is able to induce resistance and tolerance and suggests that targeting resistance and tolerance simultaneously with therapeutic IL-33 may benefit patients with systemic candidiasis. The Journal of Immunology, 2015, 194: 000–000.

Candida albicans is a commensal organism of the gastrointestinal tract and vagina. However, it can become an opportunistic pathogen in immunocompromised patients and frequently causes mucocutaneous or disseminated candidiasis (1). Furthermore, patients with innate immune defects, particularly neutropenia, are prone to systemic candidiasis because of an inability to clear the pathogen (2). In contrast, an exaggerated inflammatory response is often observed during neutrophil recovery in acute leukemia patients with systemic Candida infection (3). These observations raise important questions concerning host evolution with respect to maintaining balance between the control of fungal burden and excessive inflammation. The intestine is a prototypic organ in which this balance is well developed. For example, in the intestine, C. albicans induces innate lymphoid cells to produce IL-22, which directly targets intestinal epithelial cells and triggers the subsequent release of antimicrobial peptides and repair of damaged epithelium (1). Based on these findings, it was suggested that IL-22 is critical for host response to C. albicans by inducing resistance (initial control of fungal growth) and tolerance (rapid recovery of epithelial cell homeostasis) (1). C. albicans also can activate tolerogenic programming of gut dendritic cells and macrophages directly via its product, zymosan, or by exploiting the tryptophan metabolic pathway (4–6). Furthermore, these regulatory mechanisms might allow fungal persistence but prevent a dysregulated immune response (1). However, no intrinsic factor has been identified that controls renal tolerance in a background of C. albicans infection.

IL-33 is a multifaceted, multifunctional cytokine (7) that is believed to be released early after injury in epithelium and endothelium. IL-33 plays a variety of innate and adaptive immunity roles by acting on numerous target cells. Depending on the context, IL-33 can have inflammatory or anti-inflammatory effects. Recently, IL-33 was placed under the spotlight because it was found to act on type 2 innate lymphoid cell (ILC2s), which produce various mediators of Th2 immunity (IL-5, IL-9, and IL-13) (8), obesity (IL-5 and IL-13) (9), and tissue repair (amphiregulin) (10). Amphiregulin was shown to provide tolerance to lethal respiratory viral–bacterial coinfections independently of resistance and inflammatory pathways (11). In this study, we identified IL-33 as a cytokine to protect the host from C. albicans infection through the induction of both resistance and tolerance in the kidney.

Materials and Methods

Mice

C57BL/6 and BALB/c mice were purchased from Orient Bio-Charles River. MyD88⁻/⁻ mice with a C57BL/6 background and IL-13⁻/⁻ mice with a BALB/c background were maintained in a specific pathogen–free facility and used at 7–8 wk of age. All experiments were conducted according to the regulations issued by the Animal Committee of the University of Ulsan.

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www.jimmunol.org/cgi/doi/10.4049/jimmunol.1402986
Production of rIL-33 protein

rIL-33 protein was produced as previously described (12–14).

Fungal strains and growth conditions

C. albicans (ATCC26555) was grown in peptone dextrose extract at 30°C overnight, and aliquots were frozen at −80°C. To kill C. albicans yeasts, organisms were harvested by centrifugation, and pellets were washed twice in sterile PBS and resuspended at a density of 1 × 10⁵ cells/ml before heat killing at 90°C for 30 min.

Experimental systemic candidiasis

C. albicans were inoculated i.v. into a lateral caudal tail vein at 3 × 10⁵ CFU (lethal dose) or 1 × 10⁵ CFU (sublethal dose).

Counting CFU

Mice were euthanized, and kidneys were removed aseptically to determine fungal burdens. Harvested kidneys were homogenized in 2 ml PBS, and serial dilutions of homogenates were plated on Sabouraud agar and incubated at 37°C for 24 h. Colonies were counted, and results were expressed as log₁₀(CFU/ml) or log₁₀(CFU/organ).

Depletion of cell subsets

Neutrophil depletion was achieved by injecting 200 μg anti-Gr-1 (RB6-8C5) mAb or control rat IgG i.p. into mice 2 d before C. albicans infection. The extent of depletion was determined by staining cells with Abs to cell markers.

Real-time RT-PCR

Total RNA was extracted from kidneys or in vitro– differentiated macrophages using TRIzol (Invitrogen), according to the manufacturer’s instructions. Whole tissues were homogenized with a TissueLyser tissue homogenizer (QIAGEN), and cDNA was synthesized using SuperScript reverse transcriptase (Invitrogen). Real-time PCR was performed using SYBR Green PCR Master Mix (QIAGEN) on an ABI 7500 Fast Real-Time PCR System (Applied Biosystems). The primers used in the experiments were as follows. IL-33: 5'-CCT CCC TGA GTA CAT ACA ATG ACC-3' (forward) and 5'-GTA GTA GCA CCT GTT CTT CTT-3' (reverse); iNOS: 5'-CAC CGT GGT CTT CAC CCA GTT-3' (forward) and 5'-ACC ACT CGT ACT TGG GAT GC-3' (reverse); COX-2: 5'-AGA AAA TCG CTG CAG AA-3' (forward) and 5'-GGG CCA GCT TGG AG-3' (reverse); IL-12: 5'-CAT CGA TGA GCT GAT GCA GT-3' (forward) and 5'-CAG AEA GCC CAT CAC CCT GT-3' (reverse); Arg-1: 5'-TCA CCT GAG CTT TGA TGT CG-3' (forward) and 5'-CCT CTC TGT TGC CTT CC-3' (reverse); Ym1: 5'-ATT TGG AGC TCA ACC TTG-3' (forward) and 5'-AAT GAT TGG TCC TGC TGT GG-3' (reverse); Fizz1: 5'-TGC TGG GAT GAC TGC TAC ACC-3' (forward) and 5'-CTG GCT TCT CCA CTT CCA-3' (reverse); MR: 5'-ATG CCA AGT GGG AAA ATC TG-3' (forward) and 5'-TGT AGC AGT GGC CAT CTG AG-3' (reverse); and Pdlim1: 5'-CAT TAC TGC TCT GCC TCC TAC C-3' (forward) and 5'-GAC TCA TCG TAC TCC TGC TTT C-3' (reverse).

Preparation of kidney cells

Kidneys were perfused, minced, and placed in DMEM (Life Technologies) containing 1 μg/ml collagenase IA (Sigma–Aldrich) at 37°C for 30 min. DIGested kidney tissues were passed through a 40-μm nylon mesh and centrifuged at 900 g for 10 min. Cells were washed in PBS containing 2% BSA, suspended in 36% Percoll (Amersham Pharmacia Biotech), and gently overlaid onto 72% Percoll. After centrifugation at 900 × g for 30 min at room temperature, cells were retrieved from the Percoll interface and washed twice in DMEM and once with staining buffer (PBS containing 2% BSA and 0.1% sodium azide).

Flow cytometry

Prepared cells were blocked with 2.42g MAb in staining buffer (PBS containing 0.2% BSA and 0.1% sodium azide) at 4°C for 20 min, incubated with relevant mAbs at 4°C for 30 min, and rewashed twice with staining buffer. Flow cytometric analysis was performed using a FACSCanto II unit (BD Biosciences), and data were analyzed using FlowJo software (TreeStar).

Analysis of renal function

To determine kidney function, concentrations of creatinine and blood urea nitrogen (BUN) in sera were measured colorimetrically using the QuantiChrom Urea Assay and the QuantiChrom Creatine Assay kits (BioAssay Systems).

Histology

Kidneys were fixed in 10% (v/v) formalin, embedded in paraffin, sectioned (5 μm), stained with H&E or periodic acid–Schiff (PAS), and analyzed.

Measurement of cytokines and chemokines

Cytokines and chemokines present in total kidney homogenates and cell culture supernatants were measured using a Cytometric Bead Array kit (BD Biosciences) or by ELISA (eBioscience), respectively, according to the manufacturers’ protocols.

Culture of bone marrow–derived macrophages and adoptive transfer

Bone marrow was collected from femurs and tibias by flushing with RPMI 1640 media. Cells were washed and resuspended in DMEM supplemented with 10% FBS, 100 U/ml penicillin, and 100 μg/ml streptomycin plus 10% conditioned medium of L929 cells (a source of M-CSF) at 37°C for 5 d. After culture, ~90% of cells were F4/80+ macrophages.

M1 or M2 macrophages were polarized in the presence of 100 ng/ml LPS (Sigma–Aldrich) or 20 ng/ml IL-4 and 20 ng/ml IL-13 (Invitrogen), respectively, for 24 h. In some experiments, unpolarized M0 or polarized M2 macrophages (2 × 10⁶ cells/mouse) were injected into mice i.v. just before infection with C. albicans to test their antifungal activities.

Isolation of CD4+ T cells

Single-cell suspensions in PBS were prepared from the spleen, filtered through a sterile mesh (BD Falcon), and washed. After erythrocytes were lysed in hemolysis buffer (144 mM NH₄Cl and 17 mM Tris-HCl [pH 7.2]), the remaining cells were resuspended in MACS buffer (15 PBS containing EDTA and 3% calf serum) and incubated with anti-CD14 MicroBeads for 20 min on ice. CD4+ T cells were depleted using MACS (Miltenyi Biotec). The purity of CD4+ cells routinely reached >95%.

Phagocytosis assay

In vitro phagocytosis assays were performed as previously described (13). In brief, neutrophils from bone marrow were purified using anti-Ly6G MicroBeads, incubated in the presence of IL-33 (100 ng/ml) at 37°C for 2 h. Separately, heat-killed C. albicans was labeled with FITC, opsonized, and incubated with neutrophils at 37°C for 20 min (multiplicity of infection = 10). Phagocytosis was stopped by transferring cells into ice, and cells were washed thoroughly with cold FACS buffer. Extracellular fluorescence was quenched by adding 200 μl PBS containing 0.04% trypan blue and 1% formaldehyde. Cells containing fungi were counted by flow cytometry. Phagocytosis was expressed as the percentage of neutrophils that phagocytosed FITC-labeled C. albicans. In some experiments, in vitro– polarized bone marrow– derived macrophages (BMDMs) were used for phagocytic assays. In vivo phagocytosis assays were performed 24 h after administering 3 × 10⁸ CFU FITC-labeled live C. albicans i.v. Single-cell suspensions of kidneys were stained with anti-CD11b and anti-Ly6G mAbs in ice. The percentages of neutrophils containing phagocytosed C. albicans were determined by flow cytometry.

Fungalidal assay

Live C. albicans was opsonized with mouse serum and added to BMDMs (multiplicity of infection = 10). The mixture was incubated at 37°C with shaking for 20 min to allow the phagocytosis of live C. albicans. Cells were washed thoroughly in cold PBS, resuspended in warm DMEM, and incubated at 37°C. At the indicated times, a 200-ml sample was taken, cells were lysed in PBS containing 0.1% Triton X-100, and CFU were enumerated by plating on agar. The killing (%) was calculated as [1 − (CFU after incubation/phagocytosed CFU at the start of incubation)] × 100.

Statistical analysis

All data were analyzed using GraphPad Prism 5. Survival and unpaired data were analyzed using the log-rank test and the t test, respectively. Results are expressed as mean ± SEM. Statistical significance was accepted for p values < 0.05.

Results

IL-33 injection increased survival time after C. albicans infection

The administration of IL-33 to wild-type (WT) mice from day 1 before infection and again at 2-d intervals resulted in 100% survival
of mice infected with a sublethal dose (1 × 10^5 CFU) of C. albicans, but it had no effect in MyD88^{−/−} mice (Fig. 1A). We next examined the effects of IL-33 in WT mice challenged with a lethal dose (3 × 10^5 CFU) of C. albicans. Although IL-33 did not prevent mortality completely, it significantly prolonged survival time compared with PBS (Fig. 1B). Consistently, IL-33–injected mice experienced less severe body weight loss (Fig. 1C), and IL-33–injected kidneys appeared pinker, less swollen (Fig. 1D), and significantly lighter than PBS-injected kidneys (Fig. 1E). Gross observations also indicated that PBS-treated kidneys had many more distinguishable nodules than did IL-33–treated kidneys (Fig. 1D), which suggested that fungi had proliferated rapidly and induced extensive abscess formation in PBS-treated kidneys but were effectively cleared from IL-33–treated kidneys before visible abscesses formed. Indeed, IL-33 injection markedly lowered fungal burden in kidneys at day 3 postinfection compared with PBS injection (Fig. 1F). Histopathological analysis showed that IL-33–injected kidneys showed less severe inflammation and tissue damage and had smaller multifocal areas of abscess formation than did PBS-injected kidneys (Fig. 1G). In particular, PAS staining revealed that there were more prominent hyphae within abscesses of PBS-injected kidneys compared with IL-33–injected kidneys (Fig. 1G). Serum levels of creatinine and BUN also showed that IL-33–injected mice had less severe kidney functional impairment at days 3 and 5 postinfection (Fig. 1H). These results suggest that IL-33 protected hosts from C. albicans infection by reducing inflammation-induced renal damage and limiting fungal load.
The molecular characteristics of the IL-33–mediated suppression of inflammation were investigated by examining its effects on proinflammatory cytokines, chemokines, and neutrophil invasion. Levels of proinflammatory cytokines, including IL-6, TNF-$\alpha$, and IL-1$\beta$, reached a peak at 1 d postinfection in the kidneys of PBS-injected mice and decreased to baseline at 5 d postinfection (Fig. 2A). Levels of CXCL1 and CXCL2, CXCR2 chemokines that are required for neutrophil recruitment, peaked at 3 d postinfection and had declined at 5 d postinfection (Fig. 2B). IL-33 treatment markedly suppressed the production of these cytokines and chemokines in infected kidneys at 1 and 3 d postinfection (Fig. 2A, 2B). Consistently, IL-33 significantly inhibited neutrophil infiltration into infected kidneys at 1 and 3 d postinfection (Fig. 2C). These data show that IL-33 reduced $C.\ albicans$–induced inflammation by inhibiting the production of proinflammatory cytokines and chemokines and subsequent neutrophil recruitment.

**IL-33 promoted the phagocytic activity of neutrophils**

In a previous study, we found that IL-33 can increase neutrophil phagocytic activity in a peritoneal $C.\ albicans$ infection (13, 14). In the current study, an in vivo phagocytosis assay demonstrated that IL-33–primed CD11b$^+$Ly6G$^hi$ neutrophils had a higher capacity to phagocytose FITC-labeled $C.\ albicans$ in kidneys at 1 d postinfection (Fig. 3A). However, CD11b$^+$Ly6G$^lo$ macrophages/monocytes were poor at phagocytosing $C.\ albicans$, and IL-33 priming did not affect their phagocytic activities (Fig. 3A). Furthermore, the expression of surface ST2 on neutrophils was upregulated at 3 d postinfection versus before infection (Fig. 3B), and neutrophil depletion completely abrogated the effect of IL-33 on fungal clearance (Fig. 3C). Accordingly, fungal proliferation was uncontrollable in neutrophil-depleted kidneys (Fig. 3C), and mice depleted of neutrophils were killed rapidly by $C.\ albicans$ infection, regardless of whether IL-33 was injected (Fig. 3D). As shown in Fig. 3E, anti–Gr-1 mAb depleted neutrophils with a high efficiency in kidneys. Our results suggest that increased neutrophil phagocytic activity by IL-33 might be an important mechanism of resistance against $C.\ albicans$ infection.

**IL-33 was essential for M2 macrophage polarization during $C.\ albicans$ infection**

The skewing of M1 or M2 macrophage polarization during infection determines disease outcome. Thus, we investigated whether IL-33 could increase tolerance to $C.\ albicans$ infection by polarizing macrophages toward the M2 type. Analysis of M2/M1 ratios in kidney tissues showed that M1 responses predominated in WT mice at 1 d postinfection (Fig. 4A). However, although the dominance of M1 responses was maintained thereafter in PBS-injected kidneys, M2 responses were markedly elevated in IL-33–treated kidneys at 3 and 5 d postinfection (Fig. 4A). Real-time PCR analysis of kidneys at 3 d postinfection showed that IL-33 treatment significantly downregulated the expression of M1 marker mRNAs ($iNOS$, IL-12, and COX2) (Fig. 4B) and tended to upregulate those of M2 marker mRNAs ($Arg-1$, $Ym-1$, MR, and Fizz) (Fig. 4C). We also found that IL-33 treatment markedly increased renal levels of CCL24, but not of CCL17, at days 3 and 5 postinfection (Fig. 4D).
To further investigate the protective role of M2 macrophages in Candida infection, we transferred in vitro–polarized M2 macrophages to mice and examined their responses to Candida infection. Transfer of M2 macrophages significantly prolonged survival time compared with that of M0 macrophages (Fig. 4F). The enhancement of survival time in M2 macrophage–transferred mice seemed to be associated with increased fungal clearance, decreased production of proinflammatory cytokines, and reduced renal tissue damage (Fig. 4G–I).

These results suggest that the polarization of M2 macrophages is required for IL-33–mediated tolerance in systemic candidiasis.

**IL-33 increased tolerance to C. albicans infection through IL-13**

Th2 cytokines, such as IL-4 and IL-13, are key drivers of M2 macrophage differentiation. However, IL-13 was found to be the only Th2 cytokine (among IL-4, IL-5, and IL-13) markedly upregulated...
by IL-33 in kidneys at 3 d postinfection (Fig. 5A). In addition, IL-33 did not induce changes in the expression of macrophage polarization–affecting cytokines, such as Th17 (IL-17), Th1 (IFN-γ), and immunosuppressive cytokines (IL-10 and TGF-β) in kidneys postinfection (Fig. 5A). Intracellular staining of kidney cells isolated at 3 d postinfection showed that IL-33 increased the percentage of CD4+ T cells, but not of ILC2s, producing IL-13 (Fig. 5B). We confirmed that ST2 was expressed on renal CD4+ T cells at 3 d postinfection (Fig. 5C). In addition, IL-33 was found to stimulate isolated CD4+ T cells to secrete IL-13 in the presence of anti-CD3/28 mAbs and IL-2 (Fig. 5D). To confirm that CD4+ T cells were the major source of IL-13 in IL-33–treated mice after C. albicans infection, we depleted CD4+ T cells 1 d before infection. Indeed, adoptive transfer of WT CD4+ T cells elicited CD4+ T cells to produce IL-13 sufficient to protect hosts from C. albicans infection (15). We next investigated the mechanisms underlying these in vivo observations in vitro. It was found that IL-13 upregulated M2 marker genes in in vitro–polarized M2 macrophages (Fig. 6K), indicating the importance of IL-13–driven M2 macrophages in neutrophil-independent fungal clearance.

**Discussion**

Like many other pathogens, C. albicans can damage host tissues directly or indirectly by inducing overactivation of the host immune system (1, 2). Thus, for protection from C. albicans infection, the host immune system should check the immunopathology that leads to tissue damage without impairing the resistance mechanism associated with appropriate reductions in pathogen burden.
In this study, we found that IL-33 is able to simultaneously induce resistance and tolerance mechanisms against *C. albicans* infection: IL-33 limited *Candida* burden by directly enhancing the phagocytic activities of neutrophils and M2 macrophages, and it reduced immunopathology by inducing Th2 immunity. In our experimental system, disease severity in IL-33–injected mice seemed not to be totally dissociated from fungal burden, because IL-33 kept fungal burden in check in kidneys. However, IL-33 conferred persistent immunosuppression that involved the production of lower levels of inflammatory mediators, relatively little granulocytic infiltrate, and M2 macrophage polarization throughout the course of infection, indicating that IL-33 decreased *Candida*-induced immunopathology, leading to renal damage (16). Therefore, IL-33 provides a unique example of a factor that helps to reduce host vulnerability to damage by promoting pathogen clearance and disabling immunopathology. Furthermore, because M2 macrophages are required for tissue repair (17), it is possible that IL-33 helps the host tolerate a given *Candida* burden. Thus, we propose that IL-33–induced tolerance is associated with the capacity of the host to increase tissue repair and decrease immunopathology.

Neutrophils are a prerequisite for host defense against invasive candidiasis, but they also mediate tissue immunopathology and mortality if their infiltration into kidney tissues is not controlled during the late phase of infection (18). In our infection model, fungal proliferation reached a peak in kidneys at 3 d postinfection, when maximal numbers of neutrophils were recruited. This observation indicates that delayed neutrophil infiltration might result in early active fungal proliferation in kidneys (19), which, in turn, could induce massive neutrophil infiltration. At this time, neutrophils efficiently cleared fungi but also probably contributed to the perpetuation of immunopathology. However, infusion of large amounts of IL-33 could suppress immunopathology potently in
two ways: by effective early fungal clearance and by inducing Th2 immunity, which has an anti-inflammatory effect. This dual action of IL-33 was a surprise, because in a previous study of a model of Candida sepsis we found that IL-33 potentiates neutrophil infiltration into peritoneum via the production of CXCR2 chemokines by macrophages (13, 14). Thus, it appears that IL-33 has evolved functionally to provide a strategy whereby the kidney protects itself from damage by pathogens and immunopathology.

Although IL-33 suppressed neutrophil recruitment to kidneys after Candida infection, it is also known to activate phagocytic programming of neutrophils. In fact, IL-33 was shown to enforce TLR and Dectin-1 signaling to upregulate complement receptor 3 (CR3) in neutrophils and increase their phagocytic activity (13, 14), as well as to increase the Dectin-1–induced activation of Mac-1, a component of CR3 (20). IL-33–induced CR3 activation also results in the production of high levels of reactive oxygen species and fungicidal activity in neutrophils. Accordingly, we cannot exclude the possibility that IL-33–induced neutrophil activation can contribute to renal damage in the presence of Candida infection.

In the current study, IL-33–mediated reductions in mortality and morbidity were associated with the IL-13–mediated polarization of M2 macrophages. IL-13 levels rose sharply at 3 d postinfection when M2 macrophage polarization was maximal. The major source of IL-13 was CD4+ T cells and not ILC2s (Fig. 5B). These results show that the Th2–IL-13–M2 axis was activated by IL-33 during Candida infection and that it played a role in fungal clearance. Consistent with our findings, Katsifa et al. (21) showed that human monocytes’ phagocytosis is increased through mannose receptors in response to IL-13. Later, a series of studies delineated the mechanisms of IL-13 action in a mouse model: i.e., IL-13 increases Dectin-1 and mannose receptor expression by activating PPAR-γ, a critical transcription factor for M2 macrophage differentiation, which, in turn, increases M2 macrophage phagocytic activity (22–24). It is worth noting that human macrophages tend to differentiate into an M2 type in the presence of C. albicans (25), which suggests that animals possess safeguards at multiple stages of Th2 immunity against Candida infection.

Recently, tubular epithelial cells (TECs) have received attention as key regulators of renal sterile inflammation. Under ischemic conditions, TECs release damage-associated molecular patterns and initiate sterile inflammation (e.g., HMGB-1 and other nuclear proteins released by TECs are required for ischemia-reperfusion–induced renal inflammation) (26–28). Interestingly, these nuclear proteins bind to TEC TLR2 and TLR4; thus, they act in an autocrine manner. Our group demonstrated previously that TLR2 signaling in TECs is critical for recruiting NK cells (27) and other
flammation (29). Interestingly, TECs adopt a different approach for wave of neutrophil influx at the amplification phase of renal inflammation. CD137L signals in TECs should be delivered to induce a second inflammatory cells (H.J. Kim, H.R. Cho, and B. Kwon, unpublished observations) and benefits the host by maintaining a balance between immune competence and the establishment of immunopathology during Candida infection. We believe that our findings have important clinical implications for immunocompromised patients with an opportunistic infection.

Acknowledgments
We thank the members of H.R.C.’s and B.K.’s laboratories for help.

Disclosures
The authors have no financial conflicts of interest.

References

inflammatory cells (H.J. Kim, H.R. Cho, and B. Kwon, unpublished observations) during the initiation of renal inflammation. In contrast, CD137L signals in TECs should be delivered to induce a second wave of neutrophil influx at the amplification phase of renal inflammation (29). Interestingly, TECs adopt a different approach for managing Candida infection or ischemia-reperfusion injury. The secretion of IL-33 or chemokines by TECs seems to be governed by different signaling pathways in response to Candida infection (V.G. Tran, H.R. Cho, and B. Kwon, unpublished observations) or ischemia-reperfusion. This hypothesis is supported by our unpublished data, which shows that IL-33 is not produced by kidneys after ischemia-reperfusion. However, IL-33 was found to be secreted by endothelial cells in a model of cisplatin-induced acute kidney injury (30); in this case, IL-33 functioned as a potent proinflammatory cytokine.

In summary, the current study shows that IL-33 is a key component of the "epimmunome" (31; V.G. Tran, et al., unpublished observations) and benefits the host by maintaining a balance between immune competence and the establishment of immunopathology during Candida infection. We believe that our findings have important clinical implications for immunocompromised patients with an opportunistic infection.

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