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Local antifungal immunity in the kidney in disseminated candidiasis

Chetan V. Jawale[1], **Partha S. Biswas**[1,*]

[1]Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, USA.

Abstract

Disseminated candidiasis is a hospital-acquired infection that results in high degree of mortality despite antifungal treatment. Autopsy studies revealed that kidneys are the major target organs in disseminated candidiasis and death due to kidney damage is a frequent outcome in these patients. Thus, the need for effective therapeutic strategies to mitigate kidney damage in disseminated candidiasis is compelling. Recent studies have highlighted the essential contribution of kidney-specific immune response in host defense against systemic infection. Crosstalk between kidney-resident and infiltrating immune cells aid in the clearance of fungi and prevent tissue damage in disseminated candidiasis. In this review, we provide our recent understanding on antifungal immunity in the kidney with an emphasis on IL-17-mediated renal defense in disseminated candidiasis.

Keywords

Kidney; Candida albicans; disseminated candidiasis; innate; adaptive; IL-17

Introduction

Candida albicans is both a commensal and an opportunistic fungal pathogen of humans. Multiple manifestations of *C. albicans* infection can occur when there is a defect in the antifungal immunity [1]. Mucocutaneous forms of the disease include oropharyngeal, vaginal, and cutaneous candidiasis [2]. Disseminated candidiasis is the most severe and the third most common healthcare-associated infection with high mortality rate (~40%) [3].

*Corresponding author: Partha Sarathi Biswas, S725 BST, Div of Rheumatology and Clinical Immunology, University of Pittsburgh, S725 BST, Pittsburgh, PA 15261, Phone # 412-648-8708, Fax # 412-383-8753, psb13@pitt.edu.

Author statement

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Death due to fungal sepsis is an inevitable outcome in disseminated candidiasis [4]. Additionally, fungal hyphae invade and damage solid organs like kidneys, liver, spleen, lung and brain. The principal target organ involved in disseminated candidiasis are kidneys. This was evident in a review of 45 autopsies of patients with disseminated candidiasis, where 89% of patients had evidence of renal pathology [5]. Kidney infections can occur via hematogenous routes or from ascending spread from the bladder or urethra [6]. A mouse model of disseminated candidiasis has been established in which mice develop renal failure and septic shock following systemic spread [4,5,7–9]. Following intra-venous infection, *Candida* invades the kidney and forms 20- to 25-μm–long filaments within 2 hours post infection [10]. Interestingly, only kidneys show continuously increasing fungal burden, whereas fungal load declines in other organs [9]. Moreover, *Candida* filamentation, a key virulence factor, is seen in kidneys but not in the liver and spleen, indicating renal micro-environment plays a major role in the fungal virulence [9]. *C. albicans* hyphae proliferate in tubular space during infection and form cortical and medullary abscesses causing pyelonephritis, interstitial edema, and renal insufficiency [3,8,11]. Here, we list the recent advancement over the past 5 years in kidney-specific immunity with a focus on IL-17-driven renal defense against disseminated candidiasis.

Local antifungal immunity in the kidney

The kidney is an organ particularly susceptible to damage caused by infections and autoinflammatory conditions. Even so, renal immunology remains remarkably understudied by immunologists. Several kidney-specific factors including poor regenerative capacity of the nephrons, uremia, hypoxia and blood pressure associated changes, make it extremely challenging to study immune response in the kidney. Under homeostatic conditions, the kidneys contain a varied network of immune and non-immune cells that are ideally positioned to sense and respond to fungi [12].

1. Fungal recognition in the kidney:

Immune and non-immune cells of the kidney recognize pathogen-associated molecular patterns (PAMPs) of *Candida* yeast and hyphae by various pattern recognition receptors (PRRs). These PRRs include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide binding oligomerization domain (NOD)-like receptors, retinoid-inducible gene 1 protein (RIG1)-like receptors and complement receptors (CR). Among TLRs, TLR2 senses phospholipidomannan on the fungal surface [13], and TLR4 recognizes *O*-linked mannosyl chains in the fungal cell wall [14]. CLRs include Dectin-1, Dectin-2, and macrophage-inducible C-type lectin, DC-Sign, and mannose receptor. CLRs sense carbohydrate moieties found in the *C. albicans* cell wall, including mannans and β-glucan [3]. Accordingly, Dectin-1, Dectin-2 or Dectin-3 knockout mice showed impairment in renal fungal clearance and increased susceptibility to disseminated candidiasis [15–17]. TLR2 and TLR4 have also been implicated in renal immunity against systemic *C. albicans* infection [18]. However, recognition of fungal RNA by TLR7 has been shown to play a non-redundant role in renal antifungal activity [19]. Studies reported NLRP3 inflammasome activation by *C. albicans* hyphae [20]. Accordingly, NLRP3 and NLRP10-deficient mice showed increased susceptibility to disseminated candidiasis [21]. The melanoma differentiation-associated

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protein 5 (MDA5) senses *C. albicans* and polymorphisms in this receptor influence susceptibility to disseminated candidiasis in humans [22]. Galectin-3 recognizes β-mannans from *C. albicans* and mice lacking galectin-3 succumb to disseminated candidiasis [23]. CR3 on neutrophils recognizes β-glucans and play a role in phagocytosis of *C. albicans* [24].

2. Kidney-resident cells:

The kidney-resident myeloid cell populations comprise macrophages and dendritic cells (DCs). Phenotypically, human renal tissue-resident macrophages are $CD14^{+}CD11b^{+}CD11c^{+}CD64^{+}CD68^{-}$ [25]. The macrophages, which reside in the medullary region, phagocytose *C. albicans* yeast within the first hour after infection and produce pro-inflammatory mediators [3]. In CX3CR1-deficient mice, reduced accumulation of monocyte-derived macrophages in the kidney leads to renal failure in disseminated candidiasis. Increased susceptibility to disseminated candidiasis was also noted in patients with a polymorphism resulting in diminished CX3CR1 function [10].

Human kidneys house tissue-resident lymphocytes. Among $CD4^{+}$ T and $CD8^{+}$ T cells, the main subsets are $CD69^{+}CCR7^{-}CD45RA^{-}$ and $CD69^{+}CCR7^{-}CD45RA^{+}$, respectively [26]. NK cells in the kidney exhibit dual expression of γ- and δ-T cell receptors [12,27]. The B cell populations in kidney include IgM^{-}, IgG^{-}, and IgA^{-} cells [12]. Compared to resident myeloid cells, the role of kidney-resident lymphoid cells in antifungal immunity is less clear.

The renal tubular epithelial cells (RTECs) constitute around 80% of the total non-hematopoietic kidney-resident cells [28]. The crosstalk between RTECs and immune cells is essential for antimicrobial defense in the kidney (Fig 1). RTECs express various pathogen recognition receptors (PRRs) that sense fungal PAMPS and upregulate inflammatory cytokine and chemokine gene expression. Studies from our group showed that RTECs produce cytokines and chemokines in response to IL-17, necessary for the recruitment of innate immune effectors [29]. Consequently, mice with conditional deletion of IL-17RA in RTECs showed more severe renal damage and reduced survival during disseminated candidiasis [30]. We also demonstrated that hyphal invasion of the kidney parenchyma drives RTECs apoptosis and subsequently renal damage and dysfunction. Recently, we showed an unexpected kidney tissue protective role of IL-17 via activating the Kallikrein-Kinin System (KKS) [8]. IL-17 acts on RTECs to induce the expression of nephro-protective Kallikrein 1. Kallikrein 1 cleaves kininogen to produce kidney protective bradykinin. Consequently, therapeutic manipulation of IL-17-KKS pathway in mice restored kidney function and improved survival following disseminated candidiasis [8,30]. Thus, kidney-resident hematopoietic and non-hematopoietic cells form a very important network of antifungal immune defense in the kidney.

3. Kidney infiltrating immune effectors:

Innate immune cells

Neutrophils: During disseminated candidiasis, an innate response dominated by neutrophils is the major driver of fungal clearance in the kidney [1]. Accordingly, neutropenia is a risk factor for infection in humans and mice depleted of neutrophils are highly susceptible to disseminated candidiasis [1,31,32]. Indeed, delayed trafficking of neutrophils into kidney is

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associated with increased fungal evasion in the renal parenchyma [9]. A recent study revealed the role for IL-33 in limiting the rapid CXCL2 elevation and neutrophil aggregation resulting in impaired *C. albicans* clearance from the kidneys [33]. Moreover, Type I interferon-dependent IL-15 production from splenic monocytes drives GM-CSF production from NK cells, aiding kidney neutrophils to control fungal growth [34].

Neutrophils kill *C. albicans* by non-oxidative and oxidative mechanisms [24]. After phagocytosis of *C. albicans*, phagosomes fuse with lysosomes and neutrophil granules containing proteolytic enzymes and antimicrobial peptides (AMPs). On the other hand, activated nicotinamide adenine dinucleotide phosphate oxidase generates reactive oxygen species (ROS), which, along with other oxidants, kill fungi [35]. Additionally, neutrophils produce neutrophil extracellular traps (NETs) to kill pathogenic hyphal form [36]. The NADPH required for ROS generation by neutrophils is produced by the breakdown of glucose via glycolysis and the pentose phosphate pathway [37]. Consistently, glycolytic inhibition in neutrophils and monocytes decreased *C. albicans* killing [32,38]. We showed that kidney disease and associated uremia inhibit glucose uptake in neutrophils, which is upstream of and essential for ROS production and fungal killing in the kidney [32]. Although neutrophils are crucial for the host defense against disseminated candidiasis, but they can also drive immunopathology in the infected kidney. Studies have indicated the role of $Ccr1^+$ neutrophils in causing immunopathology in infected kidneys during later course of *C. albicans* infection. Accordingly, genetic deficiency of Ccr1 or pharmacological inhibition with the Ccr1-selective antagonist ameliorated kidney tissue damage during disseminated candidiasis [39,40]. In line with these reports, neutrophil-mediated immunopathology has been reported in individuals with renal candidiasis [41].

Monocytes and macrophages: The murine kidney-resident and kidney-infiltrating macrophages are $F4/80^{high}CD11b^{low}$ and $F4/80^{low}CD11b^{high}$, respectively [42]. The kidney-resident macrophages have unique functions in maintaining tissue homeostasis and resolving inflammation. One study indicated that $CD169^+$ kidney-resident macrophages protect the kidney during fungal infection by promoting IFNγ-dependent host resistance and neutrophil ROS activity [43]. Recently, murine kidney-resident macrophages are also implicated in cyst formation in the kidney [44]. The monocytes and macrophages also possess significant *Candida* killing capacity. Macrophage-depleted mice showed accelerated fungal proliferation in kidney [45]. Similarly, deficiency of CCR2, which is essential for monocyte recruitment to inflamed tissues, contributes to enhanced susceptibility to disseminated candidiasis [46]. The deficiency of CBLB, a E3 ubiquitin ligase that controls CLR signaling in macrophages and DCs, resulted in increased inflammasome activation, enhanced reactive oxygen species production and improved survival of mice during disseminated candidiasis. *C. albicans* competes for glucose with macrophages and triggers cell death and supplementation of glucose delayed macrophage cell death [47].

DCs: The renal DCs are present in the tubulointerstitial space and function as sentinels in homeostasis, local injury, and infection [48]. Classical myeloid DCs (cDCs) in human kidneys are $CD11c^+MHCII^+CD14^-$ and they have the ability to present antigens to T cells [48]. The renal cDCs can be divided into cDC1 and cDC2 [49]. cDC1 ($CD103^+$) constitute

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less than 5% of renal DCs, whereas majority of kidney DCs population is cDC2 [50]. Mice lacking cDC1 showed comparable susceptibility and renal fungal load in disseminated candidiasis [51]. CX3CR1 is a kidney-specific homing receptor for DCs and $CX3CR1^+$ DCs in the kidney cortex are mainly involved in mediating adaptive immune responses [52]. DCs are important for host defense during disseminated candidiasis via the production of inflammatory mediators and antigen presentation to the T cells [53,54]. Studies have indicated that DCs are involved in priming of the anti-*Candida* activity of neutrophils through an IL− 23–GM− CSF pathway, which involves NK cells [55–57]. Accordingly, GM − CSF therapy resulted in reduced mortality in patients with allogeneic hematopoietic stem cell transplant and suffering from disseminated candidiasis [58].

Adaptive immune cells: $CD4^+$ T cells are the central organizers of adaptive immune response against disseminated candidiasis [1,59].

Th1 cells: Th1 cells exert a protective role during disseminated candidiasis by virtue of IFNγ production. Hence, mice lacking IFNγ receptor are highly susceptible to infection [60]. Additionally, mice devoid of IL-18, which augments IFNγ production, are also susceptible to infection [61]. IFNγ induces nitric oxide production from neutrophils and macrophages and immunoglobulin production in *C. albicans* infection [62]. The therapeutic potential of recombinant IFNγ and IL-18 therapies have been demonstrated in mouse model and human patients [63–66].

Th2 cells: Th2 cytokines, such as IL-4 and IL-10, inhibit Th1 development and suppress phagocytic cells; therefore Th2 response favors fungal infection [67]. Overexpression of GATA-3, master transcription factor of Th2 cells, restricts IFNγ production and impairs antifungal host defense [68]. Interestingly, IL-13 is reported to increase host tolerance to *C. albicans* kidney infection by enhancing the antimicrobial function of innate cells [69].

Th17 cells: The IL-17A mRNA is produced in kidneys during the early stage of infection [30,70]. We identified that $TCR\gamma\delta^+$ T cells are the primary source of IL-17 in *C. albicans*-infected kidneys [30]. Considerable evidence suggests a role for Th17 and other innate IL-17 (IL-17A) producing cells in immunity against disseminated candidiasis. Mice deficient in IL-17RA, IL-17RC, RORγt, and IL-17A exhibit higher renal fungal load and heightened susceptibility [8,56,71,72]. Mice heterozygous for MCPIP1, a feedback inhibitor of IL-17 receptor signaling, showed enhanced resistance to disseminated candidiasis [73]. Furthermore, adenovirus or *C. albicans*-mediated overexpression of IL-17 protected mice from disseminated candidiasis [71,74]. IL-23 expression is induced in response to *C. albicans* via the CLR pathway and regulates IL-17 production by innate lymphoid cells [75]. IL-23 also protects against disseminated candidiasis by preventing myeloid cell death in infected kidneys [76]. Unlike IL-17, IL-17C or IL-17F have limited impact on survival of mice to disseminated candidiasis [77,78]. Instead, mice lacking IL-17C exhibited increased survival during disseminated candidiasis [79].

IL-17 regulates antifungal immunity through induction of a signature gene profile including antimicrobial peptides (β-defensins, calprotectin, and mucins) and neutrophil recruiting chemokines (CXCL1, CXCL5, and G-CSF). The neutrophil recruitment in kidneys of *Il17ra*

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$^{-/-}$ mice is impaired during infection [72]. One report study suggests that IL-17–dependent signaling in candidiasis does not occur in the kidney. Instead IL-17 signaling in NK cell drives GM-CSF production, which increases candidacidal activity of neutrophils in the kidney [56]. In contrast, data from our group showed that RTECs specific deletion of IL-17 signaling exacerbates kidney damage without impacting renal fungal load during disseminated candidiasis [8]. This data indicates a kidney-specific and tissue-protective role of IL-17 signaling in antifungal host defense. Another study showed that intestinal colonization with *C. albicans* drives systemic expansion of fungal-specific Th17 $CD4^+$ T cells and increased IL-17 responsiveness by neutrophils, which synergistically protect against *C. albicans* infection [80].

Conclusion

Host antifungal defense in the context of kidney is a highly neglected area of inquiry. Although it has been known that kidney-specific immune response promote protection to disseminated infection, the mechanisms by which it impacts the kidney are largely undefined. Exploring the mechanisms of local immunity in the kidney will discover downstream mediators that could act as novel drug targets for preventing kidney damage. Moreover, it may also be used to decide whether targeting these targets could be a safer and effective therapeutic option in combination with antifungal drugs. Identifying renal therapeutic targets may reveal new therapeutic strategies to counter kidney damage while sparing other vital organs from unwanted side effects.

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Highlights

- During disseminated candidiasis *C. albicans* invade and damage kidney
- No approved antifungal vaccines to prevent renal damage in disseminated candidiasis
- Kidney-resident and infiltrating immune cells control fungal burden in the kidney
- IL-17 play a renal tissue protective role in disseminated candidiasis

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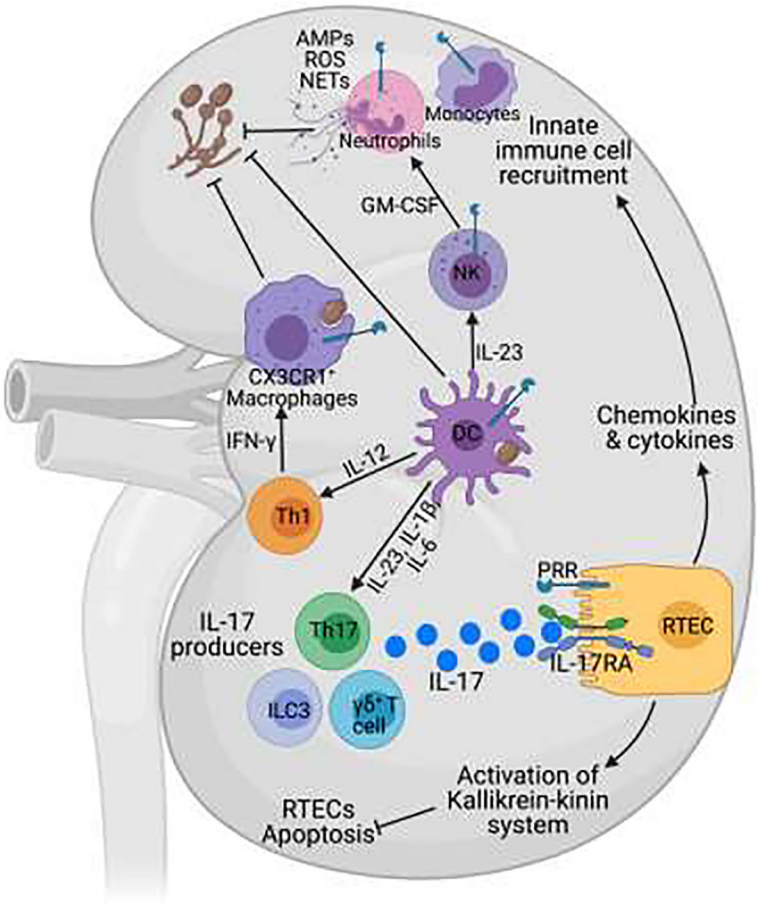

Fig 1: Antifungal immunity in the kidney.

Following fungal invasion, kidney-resident immune and non-immune cells recognize the fungi via pathogen recognition receptors (PRRs). The tissue-resident-macrophages phagocytose and clear the fungus. Dendritic cells (DCs) process fungal antigens and present it to naïve $CD4^+$ T cells to develop adaptive T helper (Th) cell responses. Th1 cells produce IFN-γ, which potentiates the phagocytic activity of macrophages. In response to *C. albicans* infection, kidney infiltrating γδ-T cells, Th17, and ILC3s are the major producers of IL-17. IL-17, in turn, binds to its receptor (IL-17RA/RC) on renal tubular epithelial cells (RTECs), activating downstream signaling events leading to expression of IL-17-responsive cytokines and chemokines genes. Innate immune cells including neutrophils recruited in response to IL-17-induced signals facilitate fungal clearance by producing antimicrobial peptides (AMPs), reactive oxygen species (ROS) and neutrophil extra-cellular traps (NETs). IL-17 also induces activation of the Kallikrein-kinin system in RTECs, which subsequently prevents apoptosis and controls tissue damage. IL-23 secreted by DCs acts on natural killer cells to produce GM-CSF, which enhances the candidacidal activity of neutrophils.