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REVIEW

Innate Immune Responses to *Sporothrix schenckii*: Recognition and Elimination

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Abstract *Sporothrix schenckii* (*S. schenckii*), a ubiquitous thermally dimorphic fungus, is the etiological agent of sporotrichosis, affecting immunocompromised and immunocompetent individuals. Despite current antifungal regimens, sporotrichosis results in prolonged treatment and significant mortality rates in the immunosuppressed population. The innate immune system forms the host's first and primary line of defense against *S. schenckii*, which has a bi-layered cell wall structure. Many components act as pathogen-associated molecular patterns (PAMPs) in pathogen-host interactions. PAMPs are recognized by pattern recognition receptors (PRRs) such as toll-like receptors, C-type lectin receptors, and complement receptors, triggering innate immune cells such as neutrophils, macrophages, and dendritic cells to phagocytize or produce mediators, contributing to *S. schenckii* elimination. The ultrastructure of *S. schenckii* and pathogen-host interactions, including PRRs and innate immune cells, are summarized in this review, promoting a better understanding of the innate immune response to *S. schenckii* and aiding in the development of protective and therapeutic strategies to combat sporotrichosis.

Keywords *Sporothrix* · *Sporothrix schenckii* · Sporotrichosis · Pattern recognition receptors · Pathogen-associated molecular patterns · Innate immune response

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Introduction

The genus of *Sporothrix* with worldwide distribution is a typical dimorphic fungus, leading to a chronic subcutaneous infectious fungal disease named sporotrichosis [1]. As genotyping technology develops, 53 species of *Sporothrix* have been identified, and only seven members were found to cause deleterious

effects on humans [2]. *S. schenckii*, *S. brasiliensis*, and *S. globosa* are the primary pathogens, and *S. schenckii* is the most studied species of a clinical clade [2]. Like other dimorphic fungi, *S. schenckii* grows as mycelia in a saprotrophic environment or culturing at 25 °C, whereas in host tissues or culturing at 37 °C, it undergoes dimorphic transition and division into pathogenic yeast cells [3]. Furthermore, the pathogenic yeast cells induce a poor pro-inflammatory compared with mycelia, suggesting an enhanced survival for *S. schenckii* [4].

The first case of sporotrichosis in the world was reported by Benjamin R.Schenck in 1898 [2]. However, sporotrichosis has now been considered an emergent health problem, owing to the increasing number of reports of *Sporothrix* infection in immunocompromised patients [5]. In addition, sporotrichosis has been classified as one of the Neglected Tropical Diseases by The World Health Organization [6]. Sporotrichosis occurs due to traumatic inoculation of materials contaminated with *Sporothrix*, causing papules, nodules, plaques, ulcers, granulomas, and crusting of the face and limbs [2, 7]. Meanwhile, primary lung disease can occur through the inhalation of spores, causing pulmonary sporotrichosis [8]. Occurrences of severe clinical forms of sporotrichosis such as disseminated [9], pulmonary [8], intravascular granuloma [10], ocular [11], and osteoarticular [12] sporotrichosis were described, especially among immunocompromised individuals [13]. Moreover, increasing evidence indicates that disseminated and extracutaneous forms of sporotrichosis occur in immunocompetent individuals [14–20]. Therefore, oral administration of antifungal agents must be maintained until the clinical cure is reached, which usually takes several months [7]. Besides, current antifungal drugs are expensive and usually invalid due to the development of drug toxicity and fungal resistance [21]. Despite treatment with antifungal drugs, patients with disseminated and extracutaneous sporotrichosis continue to have high morbidity and mortality. Among them, the mortality rates of disseminated, osteoarticular, and pulmonary sporotrichosis are 21.9% [22], 22% [12], and 42.9% [23], respectively.

The innate immune system forms the host's first line of defense against pathogens [24]. Innate immune cells such as macrophages play a vital role and are likely the primary effector cell in killing and ultimately eliminating *Sporothrix* infection [25]. More adequate approaches to treating sporotrichosis may necessitate the incorporation of immunomodulatory therapies, as the compromised status of the immune system prevents the host from responding optimally to conventional therapy. A new strategy named the *Trained Immunity-based Vaccine* indicates that immunomodulation via PRR ligands in innate immune cells could generate broad-spectrum anti-infectious formulations [26]. Therefore, effective disease control requires the engagement of host receptors by pathogen-derived PAMPs to stimulate the immune response. In this review, the ultrastructure of yeast of *S. schenckii* is reviewed, contributing to recognition of PAMPs on the cell wall. It will also highlights the role of the innate cellular immune members and the arsenal of PRRs utilized by these cells to detect *S. schenckii*, contributing to a better understanding of the innate immune in response to *S. schenckii* and assisting in developing protective and therapeutic strategies against sporotrichosis.

The Cell Wall Components of *Sporothrix*

The fungal cell wall is the first point of contact between the host and the pathogen, which also contributes to establishing communication with the environment and the host [27]. Innate immunity is triggered by the interaction between the host cell surface PRRs and the pathogen-associated molecular patterns (PAMPs) from fungi [28]. PAMPs are conserved molecular structures on the pathogen surface, whereas PRRs are conserved transmembrane or soluble receptors on host [28]. Therefore, many cell wall components of *S. schenckii* were regarded as PAMPs.

The Cell Wall Structure of *S. schenckii*

The ultrastructural data reveal that *S. schenckii* has a bi-layered cell wall structure which includes an external microfibrillar layer and an inner electron-dense layer (Fig. 1) [29].

The outer layer, i.e., fibrils, is composed of peptidorhamnomannan, a complex of molecules with a wide molecular weight range, containing 16% of peptide, 51% of mannose and 33% of rhamnose [30]. Chitin and β1,3-glucan are covered by mannan and

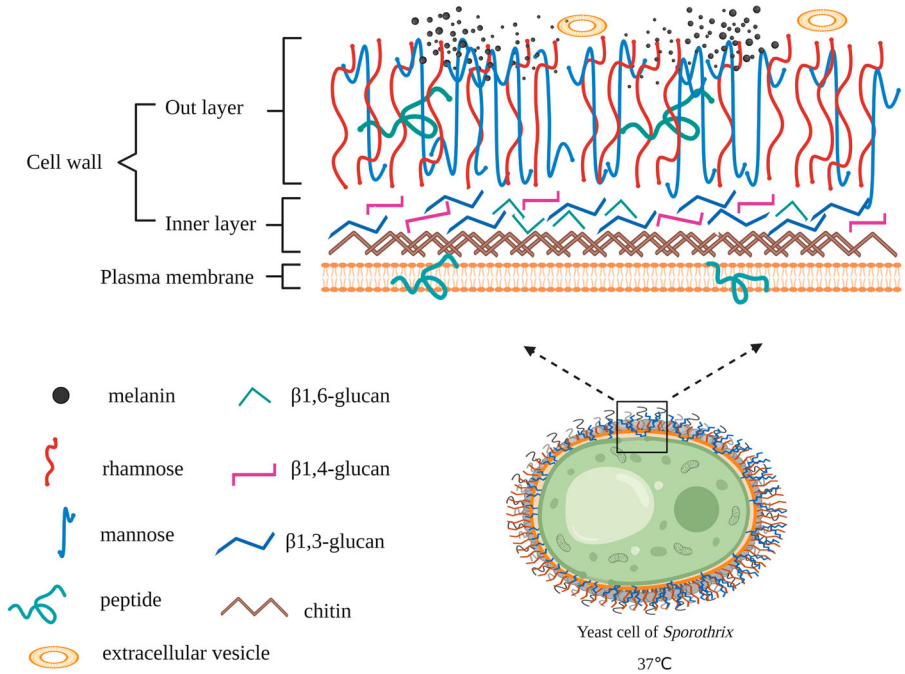

Fig. 1 A schematic diagram for pathogenic yeast cells of *Sporothrix* in host tissues or culturing at 37 °C. *S. schenckii* has a bi-layered cell wall structure, including external microfibrillar and inner electron-dense layers. The outer layer is composed of peptidorhamnomanna containing peptide, mannose and rhamnose. Meanwhile, the chitin, β1,3-glucan, β1,4-glucan and β1,6-glucan constitute the inner layer of cell wall. Melanin granules distribute on the external cell wall, and some are released into the peripheral space separated from the cell wall. Extracellular vesicles with bi-layered biological structures could be secreted by *Sporothrix* yeast cells. (Created with BioRender.com)

glycoprotein on the cell wall of *S. schenckii* sensu stricto [31–33]. Further studies demonstrate that β1,3-glucan, β1,4-glucan, β1,6-glucan and chitin constitute the inner cell wall layer [29, 32, 34].

Interestingly, glycogen α-particles could be observed in the cytoplasm adjacent to the cell wall and the plasma membrane and were localized at budding poles of yeast cells, indicating that it serves as a source of glucose, whereas it vanished after 7and/or 10 days in culture [29]. Notably, α-glucan found in other pathogenic species such as *Scedosporium*, *Pseudallescheria* and *Aspergillus* complex was not present on the cell surfaces of *Sporothrix*.spp [29, 35].

Melanin is vital to the survival of fungi and can keep them from being phagocytosed [36, 37]. Melanin granules distribute on the external cell wall, and some melanin granules are released into the peripheral space, separate from the cell wall [37, 38]. The cell wall thickness of *S. schenckii* correlates with the presence of melanin. *S. schenckii* with melanin has a thicker cell wall than *S. schenckii* without melanin [39]. Furthermore, the yeast phases of *Sporothrix* shows a reduced production of melanin compared with conidia [37].

Extracellular vesicles (EVs), bi-layered biological structures that communicate between host cells and fungi cells, are secreted from *Sporothrix* yeast cells [40, 41]. The phagocytosis index of macrophages increased after co-culture with extracellular vesicles, suggesting that EVs play a protective role during *Sporothrix* infections [41].

Adhesion to extracellular matrix proteins is crucial to the invasion of *S. schenckii*, and cell surface glycoconjugates can bind to extracellular protein fibronectin via their carbohydrate or peptide moieties [42]. *S. schenckii* has 37–92 kDa of fibronectin on the surface, which contributes to the adhesion to host cells [43]. Surprisingly, research shows that *S. schenckii* can molt sheets of intact cell wall layers and deliver into the extracellular milieu, suggesting that it can cause antigenemia or inflammation far from the original site, which maybe the immunological basis of the disseminated type [29]. However, the mechanism of cell wall-shedding remains unknown. In

general, the biofilm matrix contains polysaccharides, lipids, proteins, and nucleic acids, providing the stability of biofilms [44]. Many fungi such as *Candida*, *Cryptococcus,* and *Aspergillus* can produce biofilms that can decrease the effectiveness of antifungal therapies [45–48]. Like other fungi, *S. schenckii*, *S. globosa* and *S. brasiliensis* have the same ability to form biofilm in the filamentous phase, leading to a less susceptible to antifungal agent [49, 50]. However, it remains to explore whether yeast has the same biofilm.

The Cell Wall Related to Virulence

The proportion of cell wall components can affect the recognition of host cell PRRs, thus affecting virulence of *Sporothrix*. *S. schenckii*, *S. brasiliensis*, and *S. globosa* have a similar cell wall structure [31]. What's more, the similarity of genomes between *S. brasiliensis* and *S. schenckii* is 97.5% [51], while *S.brasiliens* is the most virulent species, followed by *S. schenckii*, and *S. globosa* is the least virulent species [52]. Cell wall proteins, kinases and heat shock proteins, extracellular and intracellular proteinases, melanin, extracellular vesicles, lipids, and biofilm were recognized as major virulent factors of *S. schenckii* [53].

The components of out cell wall contribute to the virulence of *Sporothrix*, while the exposure of inner cell wall contribute to the protective effect in host. *S. schenckii* has a thinner cell wall than *S. brasiliensis*, with lower chitin and rhamnose contents [29]. While the latest study indicated that the increased chitin in the cell wall reduces virulence [54]. Rhamnose is a vital virulence factor for *S. schenckii* in the *G.mellonella* model of infection [32]. Furthermore, the ratio of rhamnose-to-β-glucan is proportional to the virulence, while the length of rhamnomannan is inversely proportional to the virulence [55]. The carbon or nitrogen limitation of the culture medium increases β1,3-glucan exposure at the cell surface and decreases the virulence of *S. schenckii* and *S. brasiliensis*, except for *S. globosa* [56].

Host Recognition of *Sporothrix*

PRRs, expressed on host cells, are vital components of innate immunity. In addition, PRRs can recognize and initiate an inflammatory response to invading microorganisms [57]. TLRs, CLRs, NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs) are four receptor families that contribute to fungi recognition [57], especially TLRs and CLRs [58]. Fungal PAMPs contain cell wall components, such as mannan, chitin, and rhamnose. Besides, *S. schenckii* contain various potentially antigenic molecular components (Fig. 1).

Toll-Like Receptors

TLRs were first identified in Drosophila melanogaster [59]. TLRs are expressed in innate immune cells such as DCs and macrophages. There are two subfamilies of TLRs based on their localization, cell surface TLRs and intracellular TLRs. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are localized on the cell surface, while TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13 are localized in the endosome [60]. TLR-2 and TLR-4 are two of the most intensively studied receptors among TLRs.

TLR-2 plays a vital role in triggering an inflammatory response to eradicate *S. schenckii*. Macrophages from C57BL/6 TLR-2 knock-out (KO) mice significantly reduced the percentage of macrophages with internalized yeasts and reduced the release of TNF-α, IL-1β, IL-12, NO, and IL-10 (Table 1, Fig. 2) [61, 62]. After human peripheral blood mononuclear cells (PBMCs) were pre-incubated with anti-TLR2, TNF-α, IL-1β, IL-6, and IL-10 were diminished by stimulating *S. schenckii* yeast cell [31]. While IL-17 liberation is independent of TLR-2, TLR-2 absence increases the release of IL-17 and TGF-β and develops Th17 response [62]. However, research reveals that an optimal fungal clearance depends on an intact Th17 response since IL-23 decrease is accompanied by fungal burden increase [63].

TLR-4 is also crucial for developing inflammatory responses during *S. schenckii* infection [64]. Cell wall rhamnose is required for *S. schenckii* virulence and rhamnose-based oligosaccharides are ligands that interact with TLR4 [32]. Both pro-inflammatory (NO, TNF-α) and anti-inflammatory mediators (IL-10) are reduced in TLR4-deficient peritoneal macrophages after coculturing with *S. schenckii* [65]. Increased release of H_2O_2, IL-1β, IL-6, and TGF-β was found during *S. schenckii* infection on macrophages from TLR-4 deficient mice, reducing the inflammatory response [64]. Interestingly, it is CD80, CD86, and CD40 but not TLR-4 that is highly expressed on *S. schenckii* cell wall proteins (SsCWP)-

Table 1 Pattern recognition receptor (PRR) and pathogen-associated molecular pattern (PAMP) identification and outcome

PRRs	PAMP	Model system	Outcome	Citations
TLR2	LipAg	TLR2 KO (C57BL/6)	The macrophages from C57BL/6 TLR-2 KO mice cannot produce IL-1β, IL-12, TNF-α and NO	[62]
	SolAg, LipAg	TLR2 KO (C57BL/6)	The absence of TLR-2 significantly reduces the percentage of macrophages with internalized yeasts, and reduces the release of TNF-α, IL-1β, IL-12, and IL-10	[61]
	S. schenckii yeast cell	Human PBMCs	TNF-α, IL-1β, IL-6, and IL-10 were diminished upon blockage of TLR2	[31]
TLR4	rhamnose-based oligosaccharides	Macrophages incubated with *S. schenckii* with *rmlD* gene silenced	The silenced strains were more efficiently phagocytosed than the wild strain and the macrophages released a reducing level of TNFα and increasing of IL-1β and IL-10	[32]
	Lipid extraction	TLR4 KO (C3HL/HeJ)	Both pro-inflammatory mediators(NO and TNF-α) and anti-inflammatory mediators(IL-10) are reduced in TLR4-deficient peritoneal macrophages after coculturing with *S. schenckii*	[65]
	S. schenckii yeast cell	Human PBMCs	No effect the cytokine stimulation when blocking TLR4	[31]
Dectin-1	β1,3-glucan	macrophages	An elevated secretion of IL-10, NO, TNF-α and IL-1β by macrophages	[70]
	S. schenckii yeast cell	Human PBMCs	TNF-α, IL-1β, IL-6, and IL-10 were decreased after pre-incubated with laminarin, a ligand for Dectin-1	[31]
MR	*S. schenckii* yeast cell	Human PBMCs	The production of pro-inflammatory cytokines was insensitive to MR blockage	[31]
NLPR3	Alkali-insoluble fraction of *S. schenckii* yeasts	Marcrophage and splenocyte from NLRP3$^{-/-}$, ASC$^{-/-}$ and caspase-1$^{-/-}$ mice	A decreased release of IL-1β, IL-18, and IL-17, while IFN-γ release was unaffected	[81]
CR3	PRM	hMDMs	A decreased release of IL-1β by hMDM in response to *S. schenckii*	[83]
PTX3	*S. schenckii* yeast cell	hMDMs	PTX3 can enhance the clearance of pathogens by facilitating the deposition of C1q	[83]

hMDMs, human monocyte-derived macrophages; PRM, Peptidorhamnomannan; LipAg, Lipid antigen; PBMCs, Peripheral blood mononuclear cells; MR, Mannose receptor

stimulated bone marrow-derived dendritic cells (BMDCs) [66]. Furthermore, studies indicate that cytokine released by Human PBMCs pre-incubated with anti-TLR4 remained unchanged after being stimulated by *S. schenckii* yeast cells, suggesting a modest participation of TLR4 [31], The role of other TLRs, such as TLR3, and TLR9, which localizes in the endosome, have not been elucidated. In summary, TLRs contribute to *S. schenckii* recognition and elimination. Due to the potentially beneficial effects of TLRs, future research may focus on developing drugs that act as TLR agonists or ligands as potential adjuvants for vaccine formulations.

C-TYPE Lectin Receptors

CLRs, including transmembrane receptors on immune cells and soluble forms in serum, can recognize carbohydrate polymers such as mannan, glucans and chitins expressed on the fungal cell wall [67]. Dectin-1, also known as a β-glucan receptor, is the primary fungal-1,3-glucan receptor on macrophages and belongs to CLRs family, which also plays a significant role in fungal elimination removal and induction of essential receptors for cytokine production during *Sporothrix* infection [31, 68, 69]. Peritoneal macrophages could recognize β1,3-glucan by Dectin-1,

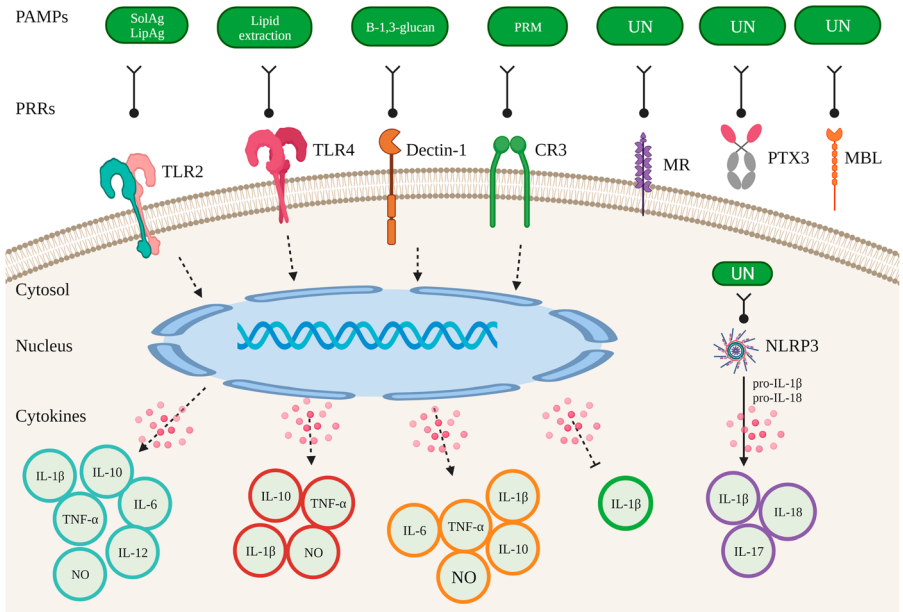

Fig. 2 SolAg and LipAg can bind to TLR2, releasing TNF-α, IL-1β, IL-12, IL-6, IL-10 and NO; TLR4 recognizes lipid extraction and releases TNF-α, IL-1β, IL-10 and NO; β1,3-glucan is recognized by Dectin-1 and results in an elevated secretion of IL-10, NO, TNF-α and IL-1β; PRM binds to CR3, leading to a decreased release of IL-1β; Alkali-insoluble fraction of *S. schenckii* yeasts binds to NLRP3 leading to a decreased release of IL-1β, IL-18, and IL-17, while IFN-γ release was unaffected. MR and PTX3 have an impact on phagocytosis but with unknown PAMPs. UN = unknown *Sporothrix* ligand for the receptor. (Created with BioRender.com)

resulting in elevated secretions of IL-10, NO, TNF-α and IL-1β [70]. In vitro, the release of TNF-α, IL-1β, IL-6, and IL-10 was decreased by PBMCs, where Dectin-1 was blocked [31]. A Dectin-1 antibody-mediated blockade assay also reduced cytokine production in infected and non-infected mice [70]. There is a study reveals that the dog with sporotrichosis which is prior resistant to itraconazole results in complete elimination of the fungus with itraconazole combined with β1,3-glucan. While the masked β1,3-glucan results a weaker recognition of fungi by innate immune cells, thus aiding in the fungi to evade from innate immune clearance [71]. β1,3-glucan can act as an immunomodulator since it can be recognized by Dectin-1 and results in the activation of host protective immunity against *S. schenckii* infection.

MR had a minor contribution to the binding and phagocytosis of conidia of *S. schenckii* compared with yeast [4]. The production of pro-inflammatory cytokines released by Human PBMCs was insensitive to the blockage of MR after coculture with *S. schenckii* yeast cells [31]. Mannose-binding lectin (MBL) and MBL-associated serine protease-2 (MASP-2) are essential proteins in the lectin pathway of the immune system [72], and decreased levels of MBL and MASP-2 have been reported in serum samples from sporotrichosis patients compared to controls [72].

Nucleotide-Binding Oligomerization Domain (NOD)-Like Receptors

The cytoplasm contains nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), which are expressed in macrophages and dendritic cells [73]. The cytosolic NLRs are crucial regulators of inflammation and responsible for IL-1β and IL-18 maturation, whose functions depend on the caspase-1 activation that can trigger a response to microbial infection and cellular damage [74]. NLRs are present in multiprotein complexes called inflammasomes, and NOD-like receptor family pyrin domain-containing 3 (NLRP3) is the most studied [75]. NLRP3 has been implicated in a wide range of diseases, including fungal diseases [76–79], and various stimuli, including danger-associated molecular patterns (DAMPs) and

PAMPs, contribute to NLRP3 inflammasome activation [80].

Recently, a study revealed that NLRP3 inflammasome linked the innate recognition of *S. schenckii* to the adaptive immune response and triggered a protective response to the host during *S. schenckii* infection. On the other hand, KO mice (NLRP3−/−, ASC−/−, and caspase-1−/−) were more susceptible to infection than the wild-type (WT). Furthermore, NLRP3 inflammasome could promote the release of IL-1β, IL-18, and IL-17 by macrophage-splenocyte coculture in vitro, leading to the elimination of fungi, while eradicating IFN-γ was unaffected [81]. Most recently, it has been reported that neodymium-doped yttrium aluminum garnet (Nd:YAG) 1,064-nm is effective in treating sporotrichosis by inducing apoptosis and pyroptosis via NLRP3/caspase-1 pathway [82].

Complement and Other Soluble Mediators

Preimmune human serum opsonization plays a critical role in optimal phagocytosis of *S. schenckii*. Internalization of yeast cells in macrophages significantly decreased in heat-inactivated serum, suggesting the role of complement components in yeast uptake [4]. The peptidorhamnomannan(PRM) is a new PAMP that is the component of cell walls of *S. schenckii* and *S. brasiliensis*, and it showed a direct interaction with the complement receptor-3(CR3). IL-1β secretion by human monocyte-derived macrophages (hMDMs) decreased when CR3 was blocked [83]. Pentraxin 3 (PTX3) is a soluble receptor that can enhance pathogen clearance by promoting C1q deposition. However, the mechanism remains to be further elucidated (Table 1, Fig. 2) [83, 84].

Effector Functions of Innate Immune Cells

Macrophages

Macrophages are the primary host protection cells, which can regulate inflammatory responses by eliminating invading fungal pathogens through phagocytosis [64]. Macrophages can adopt various phenotypes and are divided into “classic” and “alternatively” activated populations, known as M1 and M2 macrophages, respectively. In general, M1 can promote to tissue injury and result in pathogen eradication, while M2 cells contribute to tissue mimicry and repair, leading to infection persistence [85].

Macrophages undergo a phenotypic switch during the infection of *S. schenckii*. IFN-γ and IL-12 were increased in the murine model of disseminated sporotrichosis in the first two weeks, while the predominant IL-4 was presented after the fifth week [86], suggesting a classical and alternative response of macrophage activation in the early and late phase of infection, respectively. After being challenged with cell wall peptide-polysaccharide, the peritoneal exudate cells showed a predominance of M1 macrophage population with an increased NO and IL-12 production during the second week of infection, while a predominance of M2 macrophage population with an increased release of IL-10, TGF-β, and Arg-1 were present during the sixth and eighth weeks after infection [87]. *S. schenckii* infection increased the expression of disabled homolog 2 (DAB2) through JNK/c-JUN pathway and revealed a mixed M1/M2-like type of gene expression in bone marrow-derived macrophages (BMDMs), accompanied by increased of TNF-α, IL-10, and Mgl-1 and reduced IL-1β, IL-6, and Arg-1 [88].

Cryptococcus gattii and *C.neoformans* may bias the immune response toward Th2 response, helping its escape from the phagosome and resulting in disease progression [47]. Similarly, M2 macrophage populations may contribute to immune evasion, thus promoting *S. schenckii* infection [87]. Ingested conidia could survive and transform into the yeast cell in the macrophage with a complete structure [89–91]. *S. schenckii* can reverse ergosterol peroxide to ergosterol and dampen the effects on reactive oxygen species (ROS) during phagocytosis [92, 93]. This is advantageous to *S. schenckii* as an immune evasion strategy, which may be the reason for recurrent and disseminative sporotrichosis.

NO production by macrophages is a double-edged sword. It not only contributed to pathogen killing but also inhibited TNF-α release, lymphoproliferation, and MHC-2 expression, with immunosuppression consequences [86]. In addition, research proved that NO overproduction could suppress Th1 responses against *S. schenckii* and cause infection susceptibility [86, 94].

Cell wall components can suppress or promote macrophage phagocytosis. Melanin, a well-recognized virulence factor of *S. schenckii* complex, can

inhibit the innate immune functions of macrophages, such as phagocytosis and killing. MHC class II, CD86 CIITA, and PIV expressions in macrophages were inhibited when infected with a black *S. globosa* strain (MEL +) [37]. TLR2 and TLR4 receptors and the release of TNF-α and IL-6 in THP-1 macrophages were suppressed after incubation with melanin [36]. The lipid compound from the cell wall was found to inhibit the phagocytic process of macrophages while promoting the release of NO and TNF-α in macrophage culture [95].

Chitin-rich heteroglycan extracted from *S. schenckii* sensu stricto promoted fungus phagocytosis by macrophages and upregulated TNF-α expression at 24 h and IL-12 expression at 72 h after incubation [90]. Extracellular vesicles (EVs) play a crucial role in the biological process. EVs increase the phagocytic activity of macrophages and result in decreased colony-forming units [41]. In contrast, more immunoreactive components exist in EVs from *S. schenckii* compared with *S. brasiliensis* [40]. EVs have shed new light on their great potential as a therapeutic tool in modulating the immune response [40].

Dendritic Cells

DCs, known as antigen-presenting cells (APC), play an essential sentinel function by taking up antigen or infectious agents and transporting them to the lymph node for T cell recognition and the priming of immune responses [96]. In addition, DCs can sense fungi in a morphotype-specific manner and activate protective and non-protective Th cells as well as regulatory T cells, thus affecting the outcome of the infections [97].

BMDCs can phagocytize the *S. schenckii*. The expressions of CD40, CD80, and CD86 on the surface of *S. schenckii*-pulsed mouse bone marrow-derived DC increased indicating that BMDCs undergo the maturation program after stimulation with *S. schenckii*. Then, the secretion of IL-12 increased, with subsequent activation of Th1-prone immune responses [98]. *S. schenckii* of cutaneous origin is much more potent in activating DCs and induces Th1-prone immune responses, while *S. schenckii* from visceral are only weak activators for DCs with minimal induction of IFN-γ and positively induce Th2-prone immune responses [99]. The life of *S. schenckii* and its exoantigen activated BMDCs and made them capable of triggering T cell responses, and, surprisingly, the exoantigen induces an inflammatory Th17 response rather than a Th1 response [100]. SsCWP-stimulated BMDCs can induce a Th1-prone cytokine such as IFN-γ and IL-2 when cocultured with splenocytes [66].

Neutrophils

Neutrophils are the most abundant innate immunity cells in the blood and can rapidly migrate to the site of infection [101, 102]. Neutrophils represent the primary inflammatory cells associated with sporotrichosis lesions [103]. An in vitro study showed that human polymorphonuclear leukocytes (PMNLs) could phagocyte and kill yeast-phase cells of *S. schenckii* in the presence of 10% unheated serum [104], while other in vitro studies revealed that human PMNs could kill *S. schenckii* hyphae, and yeasts are resistant to be killed by neutrophils [105]. PMNs show a high capacity to bind or ingest *S. schenckii* cells, release intracellular content, and establish a pro-inflammatory environment. Meanwhile, the interaction of human PMNs with *S. schenckii* cells cannot affect fungal viability and *S. schenckii* cells can undergo dimorphic switching within PMNs [106]. Exogenous local hyperthermia at 41 °C could serve as an effective therapy for fixed cutaneous sporotrichosis, while this ability does not involve the formation of neutrophil extracellular traps (NETs) [107]. Administration of potassium iodide to regular volunteers does not increase the killing of *S. schenckii* by their neutrophils or monocytes [108]. Therefore, the role of neutrophils during the protective immune responses against *S. schenckii* is complex.

Natural Killer Cells

Natural killer (NK) cells are lymphocytes of the innate immune system, playing a critical role in the initial defense against various pathogens, including fungi [109, 110]. NK cells expand in the spleen and mature more after *S. schenckii* infection, and CD62L and KLRG1 are upregulated on NK cells. Furthermore, the fungal load in the spleens increased more than eightfold in NK cell-depleted infected mice, accompanied by an augmented systemic production of inflammatory cytokines of TNF-α, IFN-γ, and IL-6 [111], suggesting an indispensable role of NK cells

against *S. schenckii*. Recently, researchers have used expanded NK cells as therapy for invasive *Aspergillosis* resulting in a significantly reduced fungal burden in the mice model [112], providing a reference for treating sporotrichosis.

Mast Cells

Mast cells (MCs) are well recognized for their complex role in fungal infections and their critical role in allergic diseases [113]. Five PRRs have been documented in MCs: TLRs, CLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), a retinoic acid-inducible gene I (RIG-I) like receptors (RLRs), and absent-in-melanoma (AIM)-like receptors (ALRs) [114], while TLRs and CLRs are the most reported PRRs in antifungal host defense [113]. Positive or negative immunoregulatory cells can function depending on the situation [115].

MCs can improve immunity by triggering degranulation and the release of cytokines, while it seems that MCs act as negative immunoregulators in *S. schenckii* infection [113]. MC-deficient mice developed fewer skin lesions than WT mice after infection with *S. schenckii*, significantly decreasing the fungal burden [116]. The severity of cutaneous lesion of sporotrichosis was significantly reduced after depleting peritoneal mast cells [117]. Furthermore, the severity of *S. schenckii* infection in humans correlates with IL-6 and TNF levels. It has been demonstrated that MCs exacerbate mouse and human skin infection by releasing the pro-inflammatory cytokines TNF and IL-6 rather than degranulation [116, 117]. Furthermore, when the mast cells were activated by the yeast cells of *S. schenckii*, TNF-α and IL-6 could be induced by the activation of the extracellular signal-regulated kinase(ERK) signaling pathway [118].

Epithelial Cells

The epithelial lining of the skin is a protective barrier against infection [119]. The fungus's adhesion to host tissue has been identified as a critical step in colonization and invasion, including *S. schenckii* [120]. *S. schenckii* yeast cells can adhere to epithelial cells via fungal surface glycoprotein with glucose residue and mannose [121]. Antimicrobial peptides (AMPs) are released by epithelial cells and play a vital role in the innate immune system. AMPs contribute to pathogen elimination, including fungi such as *Cryptococcus neoformans* [59, 122]. Recently, AMP ToAP2D has been revealed ability to inhibit the growth of *S. globosa* and trigger apoptosis, suggesting a potential drug for treatment [123]. However, more AMPs with therapeutic effects require further research.

Epidermal keratinocytes can participate in the cutaneous inflammatory response to invading pathogens by producing pro-inflammatory cytokines and chemokines that recruit and activate neutrophils and macrophages to the infection site. Upon *S. schenckii* cells were implanted into the epidermis and dermis, keratinocytes could release IL-6 and IL-8 via TLR-2, TLR-4, and NF-κB signaling pathways [124]. Recently, it has been demonstrated that MR, CR3, TRL2, and TLR6 on keretinocytes contribute to *S.schencki* recognition, except TLR4. A pro-inflammatory environment including cytokines, chemokines, and growth factors was created to recruit other immune cells to the infection site. Besides, keratinocytes infected with *S.schencki* change the actin cytoskeleton to facilitate *S.schencki* internalization (Fig. 3) [125].

Summary and Future Prospects

Emerging data on the ultrastructure of *S. schenckii* contributes to a better understanding of sporotrichosis. Many components of the cell wall of *S. schenckii* could act as PAMPS and play a vital role in the interaction between pathogen and host. PRRs like TLRs, CLRs, NLRs, and complements are vital for recognizing PAMPs and trigger a cytokine response and phagocyte recruitment to the clearance of *Sporothrix*. As PRRs have been characterized as a protective role against sporotrichosis, further exploration of the interactions and signaling pathways is required.

The interactions between *Sporothrix* and innate immune cells play a critical role in disease progression in the host. Neutrophils are the first cells to migrate to the site of infection and can phagocytose *S. schenckii* and chemotactic for other immune cells. Macrophages play a central role in regulating the disease outcome, adopting the M1 phenotype, which promotes the clearance of *S. schenckii* and M2 phenotype, contributing to tissue remodel and repair. Dendritic cells

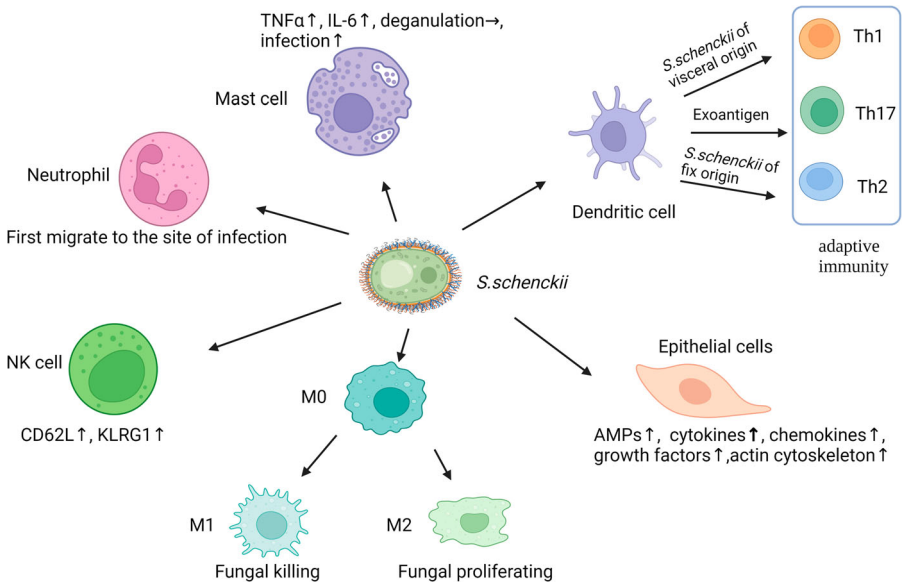

Fig. 3 Innate immune cells involved in *Sporothrix*-host interactions. Neutrophils are the first cells to migrate to the site of infection and can phagocytose *S. schenckii* as well as chemotactic for other immune cells. Macrophages play a central role in regulating the disease outcome, adopting to M1 phenotype, which promotes the clearance of *S. schenckii* and M2 phenotype, contributing to tissue remodel and repair. Dendritic cells not only phagocytose *S. schenckii* but also act as a bridge between innate and adaptive immunity. Additionally, natural killer cells, epidermal keratinocytes and epithelial cells contribute to *S. schenckii* clearance. Meanwhile, as in other diseases, MCs act as negative immunoregulators in *S. schenckii* infection. (Created with BioRender.com)

not only phagocytose *S. schenckii* but also act as a bridge between innate and adaptive immunity. Additionally, natural killer cells, epidermal keratinocytes, and epithelial cells contribute to the clearance of *S. schenckii.* While as in other diseases, MCs act as negative immunoregulators in *S. schenckii* infection [113]. However, the role of basophils cannot be excluded and warrants further investigation in sporotrichosis [116]. As the biological agents develop, monoclonal antibodies such as anti-TNF-α [126], anti-IL-17A [127], and anti-IL4/13 [128] have been increasingly used in dermatosis. Patients being treated with or prescribed biologics should be alerted since biological agents could suppress innate immunity.

This convincing evidence has emerged from studies suggesting a strong relationship between innate immune and *S. schenckii*. However, further fundamental mechanisms underlying innate immunity against *S. schenckii* remain to be elucidated. Despite adaptive immune systems, cells of the innate immune system appear to be able to gain memory characteristics after transient stimulation, resulting in an enhanced responsiveness to subsequent triggers and this phenomenon is called trained immunity [129]. The cell wall component of pathogen including LPS and β-glucan can induce trained immunity, resulting an activation of the innate immune system [130]. Therefore, we propose innovative therapeutic approaches targeting innate cells to combat sporotrichosis, especially for creating of future vaccines [21].

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights This review does not contain any studies with human participants or animals performed by any of the authors.

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