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# The immune response against *Candida* spp. and *Sporothrix schenckii*

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ABSTRACT

*Candida albicans* is the main causative agent of systemic candidiasis, a condition with high mortality rates. The study of the interaction between *C. albicans* and immune system components has been thoroughly studied and nowadays there is a model for the anti-*C. albicans* immune response; however, little is known about the sensing of other pathogenic species of the *Candida* genus. *Sporothrix schenckii* is the causative agent of sporotrichosis, a subcutaneous mycosis, and thus far there is limited information about its interaction with the immune system. In this paper, we review the most recent information about the immune sensing of species from genus *Candida* and *S. schenckii*. Thoroughly searches in scientific journal databases were performed, looking for papers addressing either *Candida*- or *Sporothrix*-immune system interactions. There is a significant advance in the knowledge of *non-C. albicans* species of *Candida* and *Sporothrix* immune sensing; however, there are still relevant points to address, such as the specific contribution of pathogen-associated molecular patterns (PAMPs) for sensing by different immune cells and the immune receptors involved in such interactions.

This manuscript is part of the series of works presented at the "V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi" (Oaxaca, Mexico, 2012).



## Respuesta inmunitaria frente a *Candida* spp. y *Sporothrix schenckii*

*Palabras clave:*
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RESUMEN

*Candida albicans* es el principal agente causante asociado a la candidiasis sistémica, una enfermedad con una tasa de mortalidad elevada. Se ha examinado cuidadosamente la interacción entre *C. albicans* y los componentes del sistema inmunitario y hoy día se ha establecido un modelo que describe la respuesta inmunitaria frente a este microorganismo. Sin embargo, apenas se conoce la de otras especies patógenas del género *Candida*. *Sporothrix schenckii* es el agente causal de la esporotricosis, una micosis subcutánea, y, hasta la fecha, solo disponemos de información limitada sobre su interacción con el sistema inmunitario. En el presente artículo revisamos la información más reciente sobre el reconocimiento inmunitario de las especies del género *Candida* y de *S. schenckii*. Se han llevado a cabo búsquedas exhaustivas en bases de datos de revistas científicas para identificar los artículos publicados sobre la interacción de *Candida* o *Sporothrix* con el sistema inmunitario. Se han hecho progresos sustanciales en el estudio del reconocimiento inmunitario de las especies de *Candida* diferentes de *C. albicans* y *Sporothrix*; sin embargo, todavía hay aspectos pertinentes que debemos abordar, tales como la contribución específica de los patrones moleculares asociados a patógenos durante el reconocimiento de estos hongos por diferentes tipos de células inmunitarias, y la identidad de los receptores inmunitarios que participan en dichas interacciones.

Este artículo forma parte de una serie de estudios presentados en el «V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi» (Oaxaca, México, 2012).



Fungal infections are among the most frequent diseases caused by pathogens, especially in hospitalized and immunocompromised populations.[5] Systemic candidiasis is associated with high mortality rates and is caused by several members of the genus *Candida*, which are opportunistic yeast-like organisms that are usually found

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as part of the mucosa and skin microbiota. Our immune system is able to properly deal with these organisms, and an imbalance in the local microbiota or a temporal or permanent loss of the immune surveillance mechanisms must be present to allow the propagation of the organism, and thus the establishment of the disease. Therefore, the study of the interaction of the immune system with *Candida* has special attention, as it is expected to find the mechanisms used by the immune system to control opportunistic pathogens. As *Candida albicans* is the most frequent species isolated from systemic infections, a significant amount of information has been gathered in the last years about its immune sensing (see for review[14,17,32,38]). It is clear now that during the early events of interaction, the innate branch of immunity plays a key role in controlling this organism and this is achieved by the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs). The PAMPs are molecules that are not synthesized by the host organism and therefore, the cell wall, which is composed of chitin, β-glucans and mannoproteins, is the main PAMP source.[14,38] Both, toll-like receptors (TLRs) and C-type lectins, participate in the sensing of *C. albicans* PAMPs: TLR2 and TLR6 recognize β1,3-glucan and phospholipomannan; *N*-mannans are recognized by mannose receptor (MR), DC-SIGN, mincle and dectin-2; *O*-mannans are sensed through TLR4, and dectin-1 is the C-type lectin in charge of the β1,3-glucan recognition.[14,38] Interestingly, chitin is a cell wall component involved in the blocking of the recognition of other PAMPs.[31] Similarly, the yeast to hypha transition has been reported as an immunoevasive strategy.[17] Despite this significant advance, we have limited information about the immune recognition of other *Candida* species.

Sporotrichosis is a mycosis distributed worldwide, especially on tropical and subtropical regions, whose etiologic agents are members of the *Sporothrix schenckii* complex.[25] The infection usually begins after a traumatic contact with contaminated material, allowing the establishment of a cutaneous or subcutaneous infection associated with regional lymphangitis and lymphadenopathy. The infection eventually may become disseminated or systemic, generally in immunocompromised patients.[25] The structure and organization of *S. schenckii* cell wall are poorly studied, and thus far the best characterized components are the peptide-rhamnomannans.[24] These are peptides modified with *N*- and *O*-glycans rich in mannose and rhamnose that are a good source of fungal antigens. Here we present the recent information generated on the immune recognition of non-*C. albicans* species of *Candida* and *S. schenckii*.

## Immune sensing of *Candida*

The immune sensing of different *Candida* species has been mainly studied using phagocytic cells and some important differences have been reported when comparing with *C. albicans*. It was reported that the uptaking rate of *Candida krusei* by human neutrophils was significantly reduced to that recorded with *C. albicans*.[42] *Candida guilliermondii*, *C. krusei* and *Candida parapsilosis* were more susceptible to be killed by murine phagocytic cells than *C. albicans* and *Candida tropicalis*.[57] In fact, these last two species were not properly recognized by peritoneal macrophages and spleen cells.[57] Furthermore, C3 and granulocyte macrophage-colony-stimulating factor (GM-CSF) production by human monocytes were assessed in presence of different *Candida* species and from these, *Candida glabrata* and *C. guilliermondii* barely stimulated their production, while *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* stimulated significant amounts of these proteins.[19] Similarly, *C. glabrata* and *C. guilliermondii* stimulated poor TNFα production by mouse peritoneal macrophages, compared with other *Candida* species.[2] Another comparative study indicates that *C. tropicalis* is more susceptible to damage by neutrophils than *C. albicans* and *C. parapsilosis*; in fact, the latter was very resistant to damage,[43] although others indicate that *C. parapsilosis* is more susceptible to killing by the macrophage oxidative metabolisms than *C. albicans*.[6,46] On the contrary, other studies suggest that different *Candida* species have the same ability to interact with human phagocytes, being uptaken and killed at similar rates.[26,29,30] This confusing information might be attributed to the pathogen-immune cell ratio used during the experiments, the immune cell type and/or the pathogen strain. Indeed, it has been recently reported that the protective role of dectin-1 during infection by *C. albicans* is strain specific due to differences in the cell wall displayed by different *C. albicans* isolates.[28] Nevertheless, it is likely that *Candida* species are differentially recognized by immune cells.

It was recently reported that human neutrophils, via galectin 3, are able to phagocyte *C. parapsilosis* yeast cells and *C. albicans* hyphae more efficiently than the yeast morphology of the latter.[22,23] The phagocytosis rate did not significantly change even though TLR2, TLR4, TLR6, CR3 or dectin-1-signaling pathways were blocked with antibodies,[22,23] suggesting galectin 3 does not interact with these pathways for *C. parapsilosis* phagocytosis. Accordingly, *C. parapsilosis* was more susceptible to reactive oxygen species (ROS)-mediated killing by human neutrophils.[23] Human monocyte-derived dendritic cells are able to phagocyte both *C. albicans* and *C. parapsilosis*, and it was demonstrated for the latter that the lack of extracellular lipases Lip1 and Lip2 significantly enhanced the phagocytic index and the killing ratio of fungal cells.[34] Moreover, these immune cells have the ability to prefer the interaction with cells from certain fungal species: upon interaction with the fungal cell, the dendritic cells form a fungipod, a structure that might help in the retention at the surface of yeast cells and thus in the overall phagocytic process, and this is strongly induced after contacting *C. parapsilosis* but not when interacting with *C. albicans*.[39] *C. tropicalis* is able to induce some fungipods, but not at the extend as *C. parapsilosis*.[39] Since the fungipod formation depends on the presence of MR,[39] these data also indicate this receptor is able to interact with the cell wall of *C. parapsilosis* and *C. tropicalis*. In agreement with the previous observation, activation of complement pathway via mannose binding lectin has been studied in both *C. albicans* and *C. parapsilosis*.[56] Both organisms were equally capable to bind this lectin and thus to activate the complement pathway that enhanced the phagocytosis by neutrophils.[56] These data indicate mannose binding lectin, as MR, recognizes similar ligands within the cell wall of both *C. albicans* and *C. parapsilosis*.

*C. albicans* hyphae are detected and discriminated from yeast cells by epithelial cells through the activation of the NF-κB and the MAPK signaling pathway that activates MKP1 and c-Fos.[33] Interestingly, other species such as *C. tropicalis*, *C. parapsilosis*, *C. glabrata* and *C. krusei* did not activate the MAPK pathway and thus an absent or diminished cytokine stimulation was observed.[20,33] Since *Candida dubliniensis* formed hyphae as *C. albicans*, it was also recognized by epithelial cells,[33] and it was suggested that hypha specific molecules recognized by host cells are absent from the pseudohypha/hypha surface of other species. Interestingly, it was reported that upon interaction of *C. parapsilosis* with engineered human oral mucosal, gingival epithelial cells responded to the pathogen expressing high levels of TLR2, TLR4, TLR6, the cytokines IL-1β, TNFα and IFNγ, and the antimicrobial peptides defensin-1, -2 and-3.[3] This apparent discrepancy with the report by Moyes et al.[33] could be explained by the fact that the *C. parapsilosis* strain used by Bahri et al.[3] was able to form hyphae.

Human neutrophils are able to differentially recognize *C. albicans* and *C. dubliniensis*, as the latter induces better fungal uptaking and cell migration than *C. albicans*. As expected, *C. dubliniensis* induces significantly more ROS production, lactoferrin

and IL-8.[52] However, *C. albicans*, but not *C. dubliniensis*, is a good stimulus for cytokine and chemokines production by macrophages and IL-17A by human monocytes, indicating that in early stages of infection *C. dubliniensis* can be better controlled, offering a possible explanation to its low virulence compared with *C. albicans*.[52]

At difference of *C. albicans* and *C. krusei* that escape phagocytosis by switching to hypha,[16] *C. glabrata* is able to duplicate within the phagolysosome until phagocyte burst, and this survival is dependent on poor phagolysosome acidification, iron acquisition via Sit1, and inhibition of ROS production.[13,40,50] Another interesting observation on *C. glabrata* includes its ability to stimulate IFN-β production by bone marrow-derived dendritic cells. This is a mechanism dependent on fungal phagocytosis, and recognition of the fungal PAMPs by the endosomal receptor TLR7.[4] This will in turn activate the induction of an IFN-I dependent response to the fungal infection. The same pathway activation was observed for *C. albicans*, but the IFN-β production was significantly lower than the stimulated by *C. glabrata*.

## Immune sensing of *S. schenckii*

The host's immune response against *S. schenckii* is not thoroughly understood as the one described for *Candida* or other human fungal pathogens, but thus far there is a significant progress in this area. The immune response against *S. schenckii* has been studied since the 70s and since then it was clear that patients with defects in the cell-mediated immune response were more susceptible to the systemic infection,[41] i.e., the immune surveillance mechanisms play a major role in controlling dissemination of this pathogen. Accordingly, athymic nude mice, but not immunocompetent animals, were more susceptible to infection with this fungus, and the former could be protected from infections by transferring immune spleen cells from normal mice.[51]

As with *Candida*, the innate branch of the immune response plays a key role in establishing a protective anti-*Sporothrix* response. Studies using mice with chronic granulomatous disease showed that ROS-based mechanisms are essential for killing phagocytosed *S. schenckii* cells by neutrophils and macrophages.[21] Furthermore, peritoneal macrophages previously activated with picibanil showed a good intracellular killing rate of the fungus, stressing the importance of them for fungal clearance.[51] However, not all the oxidative molecules produced upon fungal recognition help to clear *Sporothrix* from the tissues. Despite nitric oxide (NO) efficiently kills *S. schenckii* in vitro, in vivo studies suggest that this molecule is involved in the establishment of the disease and the immunosuppression stimulated by this organism: wild type control mice were very susceptible to infection with this organism, but not those with genetic- or drug-stimulated impaired NO production.[15] This detrimental role of NO in the immune response against *S. schenckii* was attributed to increased apoptosis of immune cells upon exposure to NO, significant high levels of IL-10, and reduced amount of TNFα production when this radical was present.[15] Furthermore, *S. schenckii* yeast cells are capable of activating both classical and alternative complement pathways, and especially the latter independently of antibody presence.[49,54] Conidia up taking by macrophages, but not yeast cells, is complement independent, indicating both morphologies are recognized by different receptors at the macrophage surface.[18] Although yeast cells were covered by C3, the specific contribution of complement activation during the anti-*Sporothrix* response still needs to be further addressed.

As other microbial pathogens, *S. schenckii* should be mainly immunorecognized by its cell wall. Recent studies indicate that *S. schenckii* cell wall is a rich source of antigens recognized by antibodies raised against this organism,[44] but we still do not know the specific contribution of its components during the fungal sensing by immune cells. Cell wall lipids have been related with stimulation of NO and TNFα, and thus with a proinflammatory response.[9] However, these lipids are also involved in the inhibition of phagocytosis by macrophages.[9] The molecular bases underlying these observations are currently unknown. Despite the specific PAMPs recognized on the surface of *Sporothrix* have not been yet identified, the specific contribution of some PRRs has been already established. TLR4 is able to recognize some molecules of lipid extracts from the yeast morphotype, leading to the production of TNFα, IL-10 and NO.[8] In agreement, TLR4-deficient mice infected with *S. schenckii* produced reduced levels of pro-inflammatory and anti-inflammatory cytokines.[47,48] TLR2 is also a key receptor during recognition of this fungus, as macrophages from TLR2-deficient mice showed reduced ability to phagocyte *S. schenckii* yeast cells.[37] Animals lacking this immune receptor produced lower TNFα, IL-1β, IL-2 and IL-10 levels than wild type controls, stressing the importance of this receptor during the immune recognition of *S. schenckii*. A recent report by Guzman-Beltran et al.,[18] suggests the participation of MR in phagocytosis of *S. schenckii* conidia by THP-1 macrophages. The ROS production was stimulated by both conidia and yeast, but only the latter was able to induce TNFα production.[18]

During sporotrichosis the host can develop adaptive immunity via macrophage activation by $CD4^+$ T cells, which release INF-γ and TNFα to boost the killing activity of macrophages against phagocytosed *S. schenckii* and driving the establishment of a Th1-based immune response.[27,53] Interestingly, it was reported that the anti-*Sporothrix* Th1 response can be modulated by different *S. schenckii* strains via differential activation of dendritic cells, being dendritic cells incubated with fungal cells from cutaneous origin better stimulus for IFN-γ production by lymphocytes than those from visceral origin.[55] Accordingly, yeast cells from visceral isolates stimulated high levels of IL-4,[55] driving the establishment of a Th2 response. Despite these evidences suggest a bias to activate the Th1 response for a good control of the microorganism, the humoral, Th2 activated response seems to play a key role in the anti-*Sporothrix* immune response.[27] The main antigen recognized by antibodies upon infection with *S. schenckii* is a 70 kDa cell wall glycoprotein, named Gp70,[35,45] and immune sensing of this molecule by antibodies seems to be a key event for the pathogen control, as *S. schenckii*-infected mice immunized with anti-Gp70 antibodies showed a significant reduction in fungal burden, even when there were deficient in T cells.[36] A possible explanation to this observation has been recently reported, indicating that this antibodies opsonise the fungal cells, increasing the ability of macrophages to phagocyte and produce pro inflammatory cytokines.[12]

Asteroid bodies are among the evasive strategies that *S. schenckii* has to avoid the immune response against it. These bodies are composed of yeast like cells that are covered by IgG and IgM molecules that may disguise the immune cells to do not recognize the fungal cells as a non-self component.[11] However, whether these antibodies are *Sporothrix* specific molecules and how they interact with the fungal cell remains to be investigated. In addition, it has been reported that the fungus has the ability to secrete proteases able to degrade different IgG types, which might contribute to the evasion of the immune system.[10] The cell wall peptide-rhamnomannan is a key fungal component to depress the immune response, especially when immune cells are exposed for prolonged periods to it, suggesting that could trigger immunological tolerance against *S. schenckii*.[7]

## Conclusions

There is a significant advance in the knowledge of the non-*C. albicans Candida* immune sensing; however, there are still relevant points to address, as the specific contribution of PAMPs

during sensing by different immune cells, the PRRs involved in those interactions, and the ability of *Candida* to change or modulate the expression of cell wall PAMPs. The immune sensing of *S. schenckii* is an area with significant activity in the last years, and it is likely that the PAMPs and PRRs involved in such recognition will be unveiled soon. Despite this, there is not information about the immune sensing of other *Sporothrix* species belonging to the *S. schenckii* complex. The study of this area might generate relevant information to explain the virulence differences observed among different *Sporothrix* species.[1]

## Conflict of interest

The authors declare no conflict of interest.

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## References

1. Arrillaga-Moncrieff I, Capilla J, Mayayo E, Marimon R, Mariné M, Gené J, et al. Different virulence levels of the species of *Sporothrix* in a murine model. Clin Microbiol Infect. 2009;15:651–5.
2. Aybay C, Imir T. Tumor necrosis factor (TNF) induction from monocyte/macrophages by *Candida* species. Immunobiology. 1996;196:363–74.
3. Bahri R, Curt S, Saidane-Mosbahi D, Rouabhia M. Normal human gingival epithelial cells sense *C. parapsilosis* by toll-like receptors and module its pathogenesis through antimicrobial peptides and proinflammatory cytokines. Mediators Inflamm. 2010;2010:940383.
4. Bourgeois C, Majer O, Frohner IE, Lesiak-Markowicz I, Hildering K-S, Glaser W, et al. Conventional dendritic cells mount a type I IFN response against *Candida* spp. requiring novel phagosomal TLR7-mediated IFN-b signaling. J Immunol. 2011;186:3104–12.
5. Brown GD, Denning DW, Levitz SM. Tackling human fungal infections. Science. 2012;336:647.
6. Brummer E, Stevens DA. Candidacidal mechanisms of peritoneal macrophages activated with lymphokines or gamma-interferon. J Med Microbiol. 1989;28:173–81.
7. Carlos I, Sgarbi D, Placeres M. Host organism defense by a peptide-polysaccharide extracted from the fungus *Sporothrix schenckii*. Mycopathologia. 1999;144:9–14.
8. Carlos IZ, Sassá MF, Graca Sgarbi DB, Placeres MCP, Maia DCG. Current research on the immune response to experimental sporotrichosis. Mycopathologia. 2009;168:1–10.
9. Carlos IZ, Sgarbi DBG, Santos GC, Placeres MCP. *Sporothrix schenckii* lipid inhibits macrophage phagocytosis: involvement of nitric oxide and tumour necrosis factor-α. Scand J Immunol. 2003;57:214–20.
10. Da Rosa D, Gezuele E, Calegari L, Goni F. Excretion–secretion products and proteases from live *Sporothrix schenckii* yeast phase: immunological detection and cleavage of human IgG. Rev Inst Med Trop Sao Paulo. 2009;51:1–7.
11. Da Rosa DW, Gezuele E, Calegari L, Goñi F. Asteroid body in sporotrichosis. Yeast viability and biological significance within the host immune response. Med Mycol. 2008;46:443–8.
12. de Lima Franco D, Nascimento RC, Ferreira KS, Almeida SR. Antibodies against *Sporothrix schenckii* enhance TNF-α production and killing by macrophages. Scand J Immunol. 2012;75:142–6.
13. Dementhon K, El-Kirat-Chatel S, Noel T. Development of an in vitro model for the multi-parametric quantification of the cellular interactions between *Candida* yeasts and phagocytes. PLoS One. 2012;7:e32621.
14. Díaz-Jiménez DF, Pérez-García LA, Martínez-Álvarez JA, Mora-Montes HM. Role of the fungal cell wall in pathogenesis and antifungal resistance. Curr Fungal Infect Rep. 2012;6:275–82.
15. Fernandes KSS, Neto EH, Brito MMS, Silva JS, Cunha FQ, Barja-Fidalgo C. Detrimental role of endogenous nitric oxide in host defence against *Sporothrix schenckii*. Immunology. 2008;123:469–79.
16. García-Rodas R, González-Camacho F, Rodríguez-Tudela JL, Cuenca-Estrella M, Zaragoza O. The interaction between *Candida krusei* and murine macrophages results in multiple outcomes, including intracellular survival and escape from killing. Infect Immun. 2011;79:2136–44.
17. Gow NA, van de Veerdonk FL, Brown AJ, Netea MG. *Candida albicans* morphogenesis and host defence: discriminating invasion from colonization. Nat Rev Microbiol. 2011;10:112–22.
18. Guzman-Beltran S, Perez-Torres A, Coronel-Cruz C, Torres-Guerrero H. Phagocytic receptors on macrophages distinguish between different *Sporothrix schenckii* morphotypes. Microbes Infect. 2012;14:1093–101.
19. Høgåsen AKM, Abrahamsen TG, Gaustad P. Various *Candida* and *Torulopsis* species differ in their ability to induce the production of C3, factor B and granulocyte-macrophage colony-stimulating factor (GM-CSF) in human monocyte cultures. J Med Microbiol. 1995;42:291–8.
20. Jayatilake J, Samaranayake LP, Lu Q, Jin LJ. IL-1α, IL-1ra and IL-8 are differentially induced by *Candida* in experimental oral candidiasis. Oral Dis. 2007;13:426–33.
21. Kajiwara H, Saito M, Ohga S, Uenotsuchi T, Yoshida S-I. Impaired host defense against *Sporothrix schenckii* in mice with chronic granulomatous disease. Infect Immun. 2004;72:5073–9.
22. Linden JR, Kunkel D, Laforce-Nesbitt SS, Bliss JM. The role of galectin-3 in phagocytosis of *Candida albicans* and *Candida parapsilosis* by human neutrophils. Cell Microbiol. 2013;15:1127–42.
23. Linden JR, Maccani MA, Laforce-Nesbitt SS, Bliss JM. High efficiency opsonin-independent phagocytosis of *Candida parapsilosis* by human neutrophils. Med Mycol. 2010;48:355–64.
24. Lopes-Bezerra L. *Sporothrix schenckii* cell wall peptidorhamnomannans. Front Microbiol. 2011;2:243.
25. López-Romero E, Reyes-Montes M del R, Pérez-Torres A, Ruiz-Baca E, Villagómez-Castro JC, Mora-Montes HM, et al. *Sporothrix schenckii* complex and sporotrichosis, an emerging health problem. Future Microbiol. 2011;6:85–102.
26. Lyman CA, Walsh TJ. Phagocytosis of medically important yeasts by polymorphonuclear leukocytes. Infect Immun. 1994;62:1489–93.
27. Maia DCG, Sassá MF, Placeres MCP, Carlos IZ. Influence of Th1/Th2 cytokines and nitric oxide in murine systemic infection induced by *Sporothrix schenckii*. Mycopathologia. 2006;161:11–9.
28. Marakalala MJ, Vautier S, Potrykus J, Walker LA, Shepardson KM, Hopke A, et al. Differential adaptation of *Candida albicans* in vivo modulates immune recognition by dectin-1. PLoS Pathog. 2013;9:e1003315.
29. Marodi L, Forehand JR, Johnston Jr RB. Mechanisms of host defense against *Candida* species. II. Biochemical basis for the killing of *Candida* by mononuclear phagocytes. J Immunol. 1991;146:2790–4.
30. Marodi L, Korchak HM, Johnston Jr RB. Mechanisms of host defense against *Candida* species. I. Phagocytosis by monocytes and monocyte-derived macrophages. J Immunol. 1991;146:2783–9.
31. Mora-Montes HM, Netea MG, Ferwerda G, Lenardon MD, Brown GD, Mistry A, et al. Recognition and blocking of innate immunity cells by *Candida albicans* chitin. Infect Immun. 2011;79:1961–70.
32. Mora-Montes HM, Ponce-Noyola P, Villagómez-Castro JC, Gow NAR, Flores-Carreón A, López-Romero E. Protein glycosylation in *Candida*. Future Microbiol. 2009;4:1167–83.
33. Moyes D, Murciano C, Runglall M, Kohli A, Islam A, Naglik J. Activation of MAPK/c-Fos induced responses in oral epithelial cells is specific to *Candida albicans* and *Candida dubliniensis* hyphae. Med Microbiol Immunol. 2012;201:93–101.
34. Nagy I, Filkor K, Nemeth T, Hamari Z, Vagvolgyi C, Gacser A. In vitro interactions of *Candida parapsilosis* wild type and lipase deficient mutants with human monocyte derived dendritic cells. BMC Microbiol. 2011;11:122.
35. Nascimento RC, Almeida SR. Humoral immune response against soluble and fractionate antigens in experimental sporotrichosis. FEMS Immunol Med Microbiol. 2005;43:241–7.
36. Nascimento RC, Espíndola NM, Castro RA, Teixeira PAC, Loureiro y Penha CV, Lopes-Bezerra LM, et al. Passive immunization with monoclonal antibody against a 70-kDa putative adhesin of *Sporothrix schenckii* induces protection in murine sporotrichosis. Eur J Immunol. 2008;38:3080–9.
37. Negrini Tde C, Ferreira LS, Alegranci P, Arthur RA, Sundfeld PP, Maia DC, et al. Role of TLR-2 and fungal surface antigens on innate immune response against *Sporothrix schenckii*. Immunol Invest. 2013;42:36–48.
38. Netea MG, Brown GD, Kullberg BJ, Gow NA. An integrated model of the recognition of *Candida albicans* by the innate immune system. Nat Rev Microbiol. 2008;6:67–78.
39. Neumann AK, Jacobson K. A novel pseudopodial component of the dendritic cell anti-fungal response: the fungipod. PLoS Pathog. 2010;6:e1000760.
40. Nevitt T, Thiele DJ. Host iron withholding demands siderophore utilization for *Candida glabrata* to survive macrophage killing. PLoS Pathog. 2011;7:e1001322.
41. Plouffe JF, Silva J, Fekety R, Reinhalter E, Browne R. Cell-mediated immune responses III sporotrichosis. J Infect Dis. 1979;139:152–7.
42. Richardson MD, Donaldson F. Interaction of *Candida krusei* with human neutrophils in vitro. J Med Microbiol. 1994;41:384–8.
43. Roilides E, Holmes A, Blake C, Pizzo PA, Walsh TJ. Effects of granulocyte colony-stimulating factor and interferon-gamma on antifungal activity of human polymorphonuclear neutrophils against pseudohyphae of different medically important *Candida* species. J Leukoc Biol. 1995;57:651–6.
44. Ruiz-Baca E, Mora-Montes HM, López-Romero E, Toriello C, Mojica-Marin V, Urtiz-Estrada N. 2D-immunoblotting analysis of *Sporothrix schenckii* cell wall. Mem Inst Oswaldo Cruz. 2011;106:248–50.
45. Ruiz-Baca E, Toriello C, Perez-Torres A, Sabanero-López M, Villagómez-Castro JC, Lopez-Romero E. Isolation and some properties of a glycoprotein of 70 kDa (Gp70) from the cell wall of *Sporothrix schenckii* involved in fungal adherence to dermal extracellular matrix. Med Mycol. 2009;47:185–96.
46. Sasada M, Johnston Jr RB. Macrophage microbicidal activity. Correlation between phagocytosis-associated oxidative metabolism and the killing of *Candida* by macrophages. J Exp Med. 1980;152:85–98.
47. Sassá MF, Saturi AET, Souza LF, De Abreu Ribeiro LC, Da Graça Sgarbi DB, Carlos IZ. Response of macrophage Toll-like receptor 4 to a *Sporothrix schenckii* lipid extract during experimental sporotrichosis. Immunology. 2009;128:301–9.
48. Sassá M, Ferreira L, Abreu Ribeiro L, Carlos I. Immune response against *Sporothrix schenckii* in TLR-4-deficient mice. Mycopathologia. 2012;174:21–30.

49. Scott EN, Muchmore HG, Fine DP. Activation of the alternative complement pathway by *Sporothrix schenckii*. Infect Immun. 1986;51:6–9.
50. Seider K, Brunke S, Schild L, Jablonowski N, Wilson D, Majer O, et al. The facultative intracellular pathogen *Candida glabrata* subverts macrophage cytokine production and phagolysosome maturation. J Immunol. 2011;187:3072–86.
51. Shiraishi A, Nakagaki K, Arai T. Role of cell-mediated immunity in the resistance to experimental sporotrichosis in mice. Mycopathologia. 1992;120:15–21.
52. Svobodova E, Staib P, Losse J, Hennicke F, Barz D, Jozsi M. Differential interaction of the two related fungal species *Candida albicans* and *Candida dubliniensis* with human neutrophils. J Immunol. 2012;189:2502–11.
53. Tachibana T, Matsuyama T, Mitsuyama M. Involvement of CD4+ T cells and macrophages in acquired protection against infection with *Sporothrix schenckii* in mice. Med Mycol. 1999;37:397–404.
54. Torinuki W, Tagami H. Complement activation by *Sporothrix schenckii*. Arch Dermatol Res. 1985;277:332–3.
55. Uenotsuchi T, Takeuchi S, Matsuda T, Urabe K, Koga T, Uchi H, et al. Differential induction of Th1-prone immunity by human dendritic cells activated with *Sporothrix schenckii* of cutaneous and visceral origins to determine their different virulence. Int Immunol. 2006;18:1637–46.
56. van Asbeck E, Hoepelman A, Scharringa J, Herpers B, Verhoef J. Mannose binding lectin plays a crucial role in innate immunity against yeast by enhanced complement activation and enhanced uptake of polymorphonuclear cells. BMC Microbiol. 2008;8:229.
57. Vecchiarelli A, Bistoni F, Cenci E, Perito S, Cassone A. In-vitro killing of *Candida* species by murine immunoeffectors and its relationship to the experimental pathogenicity. Sabouraudia. 1985;23:377–87.