

Fungal pathogen recognition by the NLRP3 inflammasome

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The relationship between host and opportunistic pathogen is a tenuous one and an injudicious response to pathogen-associated molecular patterns may result in a hostile environment to potentially beneficial commensal organisms. Therefore, discrimination between pathogenic forms, causing cellular damage, and innocuous commensal forms of microbes is critical in maintaining homeostasis. The NLRP3 inflammasome has recently been identified as playing an important role in recognition of the fungal pathogen *Candida albicans*. Here we will review these findings and discuss the role of the NLRP3 inflammasome in initiating an innate immune response to invasive *C. albicans*.

Introduction

C. albicans is a successful commensal and pathogen, highly adapted to survive on host surfaces such as mucosal tissue where it asymptotically colonizes 65% of healthy individuals. Candidemia accounts for more than 50% of fungal systemic infections and is associated with high mortality rates.¹ Although mucosal candidiasis can occur in immunocompetent individuals it is more commonly associated with immunocompromised conditions such as AIDS, and during chemotherapy or following allogenic transplantation.²

Multiple host defense systems play roles in the control of *Candida* infections depending on the type and site of infection.³ Several pattern recognition receptors have been implicated in mediating innate immune responses to *C. albicans*. Toll-like receptor 2 (TLR2) and TLR4 can both recognize *Candida*. In a disseminated

candidiasis model, TLR4 was shown to be protective,⁴ whereas TLR2 augmented IL-10 production and exacerbated disease.⁵ Recently, TLR9 has also been shown to be involved in anti-*Candida* host responses by mediating a cytokine response after stimulation with *C. albicans* DNA.⁶ However TLR9 was not crucial in an in vivo model of disseminated candidiasis.^{6,7} Other types of pattern recognition receptors are also involved in *C. albicans* recognition including lectins on macrophages (M ϕ), dendritic cells (DC), keratinocytes⁸⁻¹³ and integrins on leukocytes.¹⁴ Recently, several studies have suggested that C-type lectins are the major receptors in antifungal defense. Dectin-1 recognizes fungal β -(1,3)-glucans and possesses a cytoplasmic immunoreceptor tyrosine-based activating like motif (ITAM) which mediates immune signaling in response to *C. albicans* via spleen tyrosine kinase (syk) and caspase recruitment domain protein 9 (CARD9).¹⁵⁻¹⁸ Another C-type lectin, Mincle, plays a role in M ϕ responses to *C. albicans* and Mincle-deficient mice display an increased susceptibility to *C. albicans* infection in vivo.¹⁹ The mannose receptor (also a C-type lectin) recognizes mannan and mannoprotein plays an important role in phagosome sampling, cytokine production and adaptive immune response.^{20,21} *C. albicans* associates with the mannose receptor after phagocytosis at a late stage of phagosomal maturation and is not necessary for *C. albicans* uptake.²⁰

The multitude of receptors involved in host recognition of *C. albicans* may reflect the vast repertoire of phenotypic features that *C. albicans* is able to display during the course of an infection. *C. albicans* dimorphism, also called bud-hyphae transition, is the most studied and results in a

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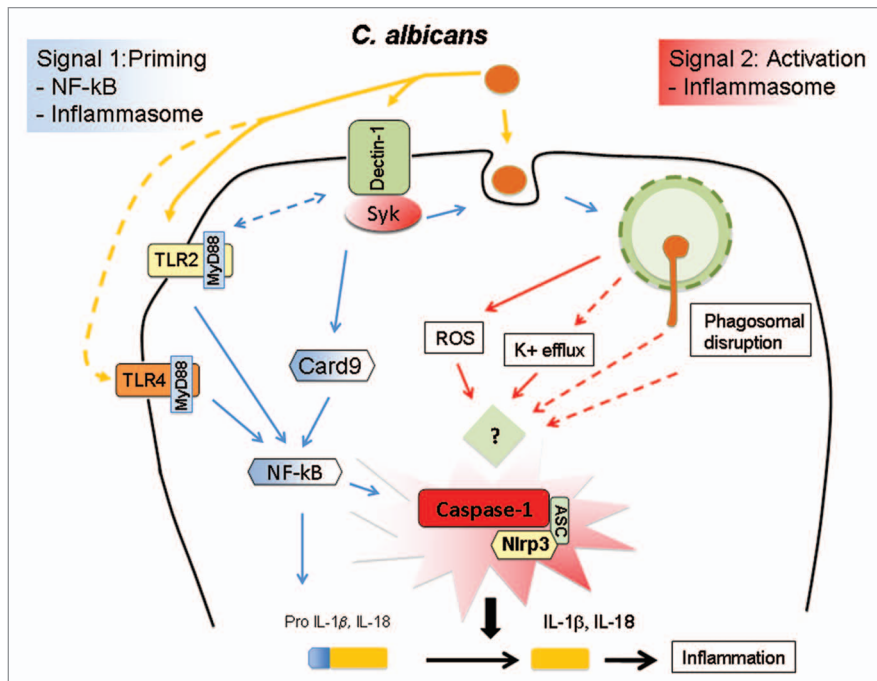


Figure 1. Model of NLRP3 inflammasome activation mediated by *C. albicans*. Signal 1 (blue arrows) and signal 2 (red arrows) are necessary for the assembly and activation of a multiprotein complex composed of NLRP3, the adaptor molecule ASC and the cysteine protease Caspase-1 resulting in IL-1 β processing and secretion. Several pathways have been shown (plain line) or suggested (dashed line) to be important for signal 1 and signal 2 generated in response to *C. albicans*. However it is likely that these pathways converge on an unknown endogenous molecule that serves as the direct ligand necessary for NLRP3 inflammasome activation.

differential interaction with the host innate response, affecting receptor recognition, cytokine production and cell-mediated responses. Indeed, killed blastospores have been shown to signal through TLR2 and 4 whereas killed hyphae predominantly use TLR2 resulting in a non-protective response.^{17,22} Interestingly, while Dectin-1 exclusively associates with the *C. albicans* yeast form, Dectin-2 preferentially binds to hyphae.¹³ The interaction of yeast and hyphae forms of *C. albicans* with DCs also greatly influences the subsequent T cell responses that follow.²³

Recently we, and others, have shown that the cytosolic nucleotide-binding domain leucine-rich repeat containing receptor (NLR) family member NLRP3 (also known as NALP3, Cryopyrin and CIAS1) is a key player in host defense against *C. albicans*.²⁴⁻²⁶ Infection of M ϕ and DCs with *C. albicans* results in activation of the NLRP3 inflammasome with the resultant activation of caspase-1 and processing and secretion of IL-1 β . IL-1 β mediates a strong protective Th1

response against *C. albicans* infection and IL-1R (the receptor for IL-1 β) is crucial for host defense against disseminated *C. albicans*.^{25,27,28} In addition, polymorphisms in the gene coding for NLRP3 have been associated with recurrent vulvovaginal candidiasis.²⁹ The cytosolic nature of NLRP3 is of great importance in understanding the immune regulation occurring during host-opportunistic pathogen relationships. In this review we will particularly focus on the role and mechanism of NLRP3 inflammasome activation in response to *C. albicans*.

***C. albicans*-Mediated Activation of the NLRP3 Inflammasome**

The NLR family of molecules is a newly described group of intracellular receptors that drive both inflammatory and cell death pathways. A number of NLR molecules form inflammasomes, which are multiprotein complexes capable of activating caspase-1 and ultimately resulting in the processing and secretion of IL-1 β

and IL-18. As intracellular receptors, the NLR family is in a prime location to detect danger signals associated with host stress and may therefore play a critical role in recognizing the transition from commensal to pathogen. The NLRP3 inflammasome can be activated in response to a large number of unrelated stimuli: (1) microbial (viruses, bacteria, yeast, bacterial toxins, bacterial motifs), (2) endogenous (ATP, monosodium urate crystals, calcium pyrophosphate dihydrate crystals, β -amyloid), and (3) exogenous (UV, alum, silica, asbestos) (reviewed in ref. 30). Activation of the NLRP3 inflammasome requires a two-step process described as signal 1 (priming) and signal 2 (activation). Signal 1 can be initiated by numerous stimuli and importantly these can be both microbial and non-microbial in origin.^{31,32} Given the varied number of agents that can contribute to signal 2 in NLRP3 inflammasome activation, it is unlikely that they are direct ligands for NLRP3 but instead induce a common endogenous molecule that is recognized by NLRP3. While it is accepted that *C. albicans* induces caspase-1-mediated IL-1 β secretion in a NLRP3 dependent manner,^{24-26,33} the precise pathways involved in NLRP3 inflammasome activation are yet to be defined (Fig. 1).

Signal 1. Signal 1 serves two functions, in addition to stimulating the production of pro-IL-1 β via the NF κ B pathway, it is also a prerequisite for inflammasome priming. As mentioned above, *C. albicans* is recognized by several receptors such as TLR4, TLR2, Dectin-1, Dectin-2, the mannose receptor, and Mincle^{17,19} that can potentially activate NF κ B. However, signaling through Dectin-1 and syk/CARD9 appear to be the predominant pathways involved in *C. albicans*-induced pro-IL-1 β production.^{24,25} Syk signaling was necessary for *C. albicans*-induced activation of the NLRP3 inflammasome,²⁴ however β -glucan and zymosan that are also direct activators of this pathway failed to rapidly activate the NLRP3 inflammasome.^{25,26} The role of syk in NLRP3 inflammasome activation has also been described for malarial hemozoin³⁴ and uric acid crystals.³⁵ Syk signaling is however dispensable for NLRP3 inflammasome activation by

pore forming toxins and ATP²⁴ suggesting that syk involvement may be specific to particulate activators. Together these studies reinforce the role of syk in priming the NLRP3 inflammasome for activation by *C. albicans*. CARD9 is however dispensable for NLRP3 inflammasome activation in response to *C. albicans* as priming with the TLR4 agonist LPS can bypass the requirement for CARD9.²⁴ Non-microbial agents can also act as signal 1 as demonstrated by recent studies showing that TNF α , hyaluronan, biglycan and HMGB1 can all serve a priming role in NLRP3 inflammasome activation.^{31,32,36}

The ability of *C. albicans* itself to directly provide signal 1 is dependent on the cell type infected. For bone marrow-derived dendritic cells (BMDC) and thioglycollate-elicited M ϕ , *C. albicans* was able to both prime (signal 1) and activate (signal 2) the NLRP3 inflammasome.^{24,25,37} In contrast, bone marrow-derived macrophages (BMDM) required an independent priming step prior to infection with *C. albicans* in order to achieve NLRP3 inflammasome activation.^{24,26} These findings in BMDM paralleled earlier studies that demonstrate Dectin-1 signaling alone is not sufficient to activate NF κ B and induce TNF α production.³⁸ This lack of responsiveness in M ϕ was later attributed to a differential use of CARD9 by Dectin-1 in M ϕ as compared to DCs.³⁹ One notable difference in the generation of BMDM compared to BMDC is their exposure to GM-CSF. Exposure of M ϕ to either GM-CSF or IFN γ resulted in increased responsiveness to β -glucan⁴⁰ by activating a CARD9-dependent pathway in M ϕ .³⁹

In contrast to DCs²⁴ the production of pro-IL-1 β by thioglycollate-elicited M ϕ was MyD88 dependent.²⁵ Similarly, β -glucan induced TNF α production has been previously shown to synergize with TLR signaling in M ϕ ⁴¹ while β -glucan induced TNF α production was found to be MyD88 independent in DCs.¹⁶ The marked differences in the requirements for NLRP3 inflammasome activation between divergent cell types is highlighted in a recent study by Pelegrin and Surprenant in which ATP-mediated NLRP3 inflammasome activation seen in

M1 polarized M ϕ was diminished by M2 polarization.⁴²

Signal 2. The rapid activation of the NLRP3 inflammasome by *C. albicans* required the presence of live yeast^{24,26} and was not dependent on ATP release, either from *Candida* or the phagocyte, as P2X7 receptor-deficient cells were capable of secreting IL-1 β in response to *C. albicans*.²⁴⁻²⁶ Interestingly, an overnight or prolonged incubation with formalin fixed *C. albicans*²⁵ or β -glucans (zymosan, curdlan)³³ was able to induce (although in a weaker manner) NLRP3 dependent IL-1 β secretion by thioglycollate-elicited peritoneal M ϕ . The different magnitudes and kinetics of NLRP3 inflammasome activation seen between live and killed (or cell wall components) *C. albicans* suggests that different signaling pathways are being utilized.

Phenotypic plasticity is an important part of *C. albicans* virulence and its ability to transition between yeast and filamentous form have been shown to drastically impact host responses. Hyphal filaments were poor inducers of NLRP3 inflammasome activation and resulted in a significantly lower amount of IL-1 β from BMDM, BMDC and peritoneal M ϕ .²⁴⁻²⁶ It is not clear why *C. albicans* hyphae fail to induce robust NLRP3 inflammasome activation, but this may be linked to ineffective phagocytosis of hyphae or lack of surface molecules required to trigger NLRP3 inflammasome activation. Several studies have shown that phagocytosis of particulate activators is necessary for NLRP3 inflammasome activation.³⁰ Similarly, phagocytosis of *C. albicans* is also required for NLRP3 inflammasome activation.²⁶ It has been postulated that the uptake of particulates may result in lysosomal disruption and therefore expose to the cytosol endogenous molecules normally found in a sequestered location.⁴³ Although hyphae did not possess stimulatory properties, the ability of *C. albicans* to transition from yeast to hyphal form was essential for NLRP3 activation as the *C. albicans* *efg1 Δ / Δ cph Δ / Δ* double mutant and the opaque phenotype of strain WO-1, locked in a yeast phase, were unable to activate NLRP3.²⁶ Interestingly, *C. albicans* phagosomal escape and disruption are mediated by a switch to a filamentous

form after internalization⁴⁴ thereby releasing endogenous molecule into the cytosol. Release of the lysosomal protease cathepsin B into the cytosol has been proposed to be necessary for IL-1 β secretion by particulate activators of NLRP3.^{45,46} Although the cathepsin B inhibitor Ca-074-me inhibited *C. albicans*-induced activation of NLRP3 inflammasome in BMDM,²⁶ Gross and colleagues²⁴ demonstrated that NLRP3 activation was not affected in BMDC from cathepsin B-deficient mice suggesting that the inhibition seen with Ca-074-me may be due to off-target effects of the inhibitor. A commonality shared by ATP, pore-forming toxins and particulate mediated NLRP3 inflammasome activation is its dependency on a potassium efflux and the generation of reactive oxygen species. As expected, *C. albicans*-mediated NLRP3 inflammasome activation was dependent on both potassium efflux and reactive oxygen species production (Fig. 1).²⁴

Role of the NLRP3 Inflammasome in the Pathogenesis of *C. albicans* Infections

The NLRP3 inflammasome plays an important role in a disseminated model of Candidal infection. Mice deficient in NLRP3 infected with *C. albicans* displayed diminished serum IL-1 β , reduced survival²⁴ and higher fungal burdens in kidney, spleen, liver and lung.²⁴⁻²⁶ Using a murine model of oral *C. albicans* infection Hise and colleagues further demonstrated that IL-1R, NLRP3, and the inflammasome components ASC and caspase-1 were necessary to prevent systemic dissemination of *C. albicans*. The role of NLRP3 and caspase-1 in the local mucosal colonization, unlike IL-1R and ASC, were limited.²⁵

Interestingly, polymorphism in the gene coding for NLRP3 have been associated with recurrent vulvovaginal candidiasis²⁹ underscoring the role of NLRP3 in mucosal homeostasis. However, it has been hypothesized that distinct defense mechanisms regulate innate immunity in vulvovaginitis, oropharyngeal candidiasis and systemic candidiasis as vaginitis and systemic infection in HIV positive individual are far less common

that oropharyngeal candidiasis.³ NLRP3 may play an important role in differentiating commensal organisms from pathogenic ones. Extracellular pathogen-associated molecular patterns may ready phagocytes for activation through TLR stimulation. However, only once an organism becomes a true threat, as determined by cellular invasion resulting in cellular stress and damage, is the NLRP3 inflammasome pathway activated. Because *C. albicans* possesses the ability to modulate NLRP3 activation via phenotypic plasticity, the differential interaction with various immune cells and the route of infection (mucosal or systemic), there is no doubt that future studies will use this powerful model to unravel the identity of NLRP3 ligand and to study the impact of NLRP3 inflammasome in the control of opportunistic pathogens. The complexity of NLRP3 signaling and the multiple requirements needed to achieve a rapid and robust response reflects the tight regulation that makes inflammasome activation a secure, stable and highly specific pathway to initiate innate immune responses to invading organisms.

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