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ITAM Receptor Signaling and the NLRP3 Inflammasome in Antifungal Immunity

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Abstract
Introduction Infections with fungi can cause systemic life-threatening diseases in immunocompromised individuals like cancer or AIDS patients. Recent work has uncovered essential roles for C-type lectin pattern recognition receptors, spleen tyrosine kinase (SYK) and the cytosolic NLRP3 inflammasome in innate antifungal immunity. Upon fungal infection, SYK is activated by several ITAM-containing or ITAM-coupled C-type lectin receptors on myeloid cells leading to the production of pro-inflammatory cytokines including IL-1β to initiate antifungal responses. Mature IL-1β production requires in addition to the synthesis of pro-IL-1β a cleavage of the precursor protein by the inflammatory Caspase-1 which is controlled within the NLRP3 inflammasome.
Scope Here, we discuss how ITAM receptor signaling and NLRP3 cooperate for the induction of antifungal immunity.

Keywords ITAM receptors · SYK · CARD9 · inflammasome · NLRP3 · IL-1β

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The NLRP3 Inflammasome

"Inflammasomes" are intracellular multi-protein complexes that control activation of inflammatory caspases such as Caspase-1 and the secretion of bioactive IL-1β and IL-18. Recent work has characterized distinct types of inflammasomes that contain specific danger sensors which directly or indirectly couple to pro-Caspase-1 to trigger Caspase-1 activation [1, 2]. Among these are the NLRP1 (also known as NALP1 or DEFCAP) inflammasome which mediates IL-1β secretion in response to Anthrax lethal toxin [3], the AIM2 inflammasome [4–7] that activates Caspase-1 upon DNA virus infection, the RIG-I inflammasome that triggers caspase-1-dependent inflammasome activation in response to certain RNA viruses [8] and the multifunctional NLRP3 inflammasome that can respond to many distinct stimuli [1].

Several recent studies reported that the NLRP3 inflammasome is the essential platform for Caspase-1 activation in response to fungal recognition [9–11]. Yet, the NLRP3 inflammasome is not specific for fungi. NLRP3 can be activated by multiple distinct exogenous and endogenous triggers which include crystals (uric acid, silica and asbestos [12–14]), bacteria (Staph. aureus, Neiseria meningitides [15]), bacterial pore forming toxins [16], certain DNA (Adenovirus) [17] and RNA viruses (Influenza virus) [18–20], vaccine adjuvants (Alum) [21] and fibrillar amyloid-β [22]. At the molecular level, it is still unclear how all these distinct stimuli activate NLRP3.

The NLRP3 protein is composed of a C-terminal region with a series of leucin rich repeats (LRRs), a central nucleotide domain termed the NACHT domain (also referred to as NOD domain), and an N-terminal effector domain (a pyrin domain (PYD) [1] (Fig. 1). Upon stimulation, NLRP3 presumably undergoes a conformational change to initiate complex formation. The leucine-rich repeats of NLRP3 are

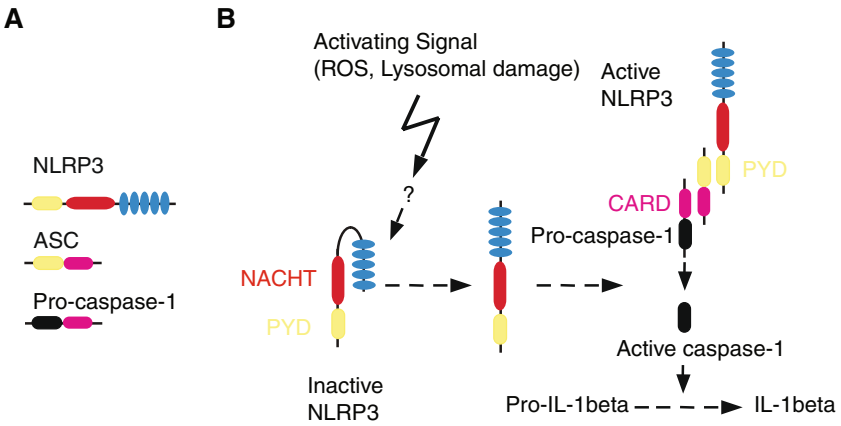

Fig. 1 NLRP3 inflammasome activation. (**A**) Domain organization of NLRP3, ASC and Caspase-1. NLRP3 consists of three distinct domains: the ligand-sensing leucine-rich repeats (LRRs); the NACHT domain and the N-terminal effector domain, a pyrin domain (*PYD*). ASC contains a N-terminal PYD and a C-terminal caspase recruitment domain (*CARD*) and is essential for NLRP3 inflammasome formation. Caspase-1 has a CARD domain followed by a domain containing the catalytic residue cysteine. (**B**) Various exogenous and endogenous signals ("Signal") can activate NLRP3 which presumably undergoes a conformational change to initiate complex formation. The leucine-rich repeats of NLRP3 are thought to sense putative ligands thereby leading to the self-oligomerization of the NACHT domain. This results in homotypic interactions between the PYD and CARD domains found in the inflammasome-forming proteins and ultimately leads to autocatalytic cleavage and activation of Caspase-1 and subsequent Caspase-1 mediated processing of pro-IL-1β into biologically active IL-1β. (Abbreviations: *LRRs* leucine-rich repeats, *CARD* caspase recruitment domain, *PYD* pyrin domain, *NACHT* domain conserved in NAIP, CIITA, HET-E and TP1, *ASC* apoptosis-associated speck-like protein containing a carboxy-terminal CARD)

supposed to sense putative ligands thereby leading to the self-oligomerization of the NACHT domain [23] and subsequent inflammasome assembly. For Caspase-1 activation, NLRP3 utilizes the adapter protein ASC which contains a N-terminal PYD and a C-terminal CARD domain [1]. Following oligomerization of the NACHT domains, the PYD of NLRP3 is then exposed and forms homotypic interactions with the PYD of ASC. Subsequently, the CARD domain within ASC binds to and recruits Caspase-1 via CARD–CARD interaction to finally form the active NLRP3 inflammasome [24] (Fig. 1**)** which is essential for the secretion of mature IL-1β.

Earlier experiments have shown that IL-1β plays an essential role in antifungal immunity [25]. Since IL-1β is a highly pyrogenic cytokine its production is tightly controlled by transcriptional and post-transcriptional signals. NF-κB mediated gene transcription is essential for the synthesis of the IL-1β precursor pro-IL-1β (signal 1). In addition, a second stimulus (signal 2) drives the proteolytic processing of pro-IL-1β into mature bioactive IL-1β by Caspase-1 containing inflammasomes [1, 24]. Work over the last year has uncovered an important role for the NLRP3 inflammasome in IL-1β generation upon fungal infection and subsequent host defense.

ITAM Receptor Signaling upon Fungal Recognition

To trigger antifungal defense, the innate immune system depends on germ line encoded pattern recognition receptors (PRRs) that bind conserved molecular patterns on pathogens (pathogen associated molecular patterns, PAMPs). The family of PRRs consists of the transmembrane Toll-like receptors [26] and C-type lectin receptors (CLRs) [27] as well as intracellular sensor like members of the NOD-like receptor (NLR) family [1], RIG-I like helicases [26] and others. In particular, CLRs are important for fungal detection. [28–30]. Several CLRs engage the spleen tyrosine kinase SYK for signal transduction and this enzyme is key for antifungal immunity (generation of reactive oxygen species (ROS) and de novo gene transcription for the production of cytokines and chemokines). Best characterized among these is Dectin-1 [27], which is expressed on myeloid cells (myeloid DCs, monocytes) and B cells [27, 31]. Dectin-1 recognizes β-glucans which are present in the cell walls of pathogenic fungi like *Candida albicans* and others [31]. Dectin-1 contains a ligand binding ectodomain and an intracellular signaling tail with an atypical immunoreceptor tyrosine-based activation motif (ITAM) with a single YxxL motif. Upon ligand recognition, the cytoplasmic signaling domains of Dectin-1 are phosphorylated by SRC tyrosine kinases leading to a recruitment and activation of the kinase SYK for further cell activation.

Dectin-1 activates via SYK several transcription factors including NF-κB for the production of pro-inflammatory cytokines and also of pro-IL-1β [9, 32, 33]. In addition, SYK has a key function in the generation of ROS upon Dectin-1 signaling [34]. Essential for Dectin-1/SYK-mediated cytokine production via NF-κB is the Caspase recruitment domain containing adapter

protein CARD9. CARD9 in turn cooperates with the adaptors BCL-10 and MALT1 to form a complex that induces the activation of the canonical IκB kinase-dependent NF-κB pathway in a cell-type specific manner [32, 35, 36]. Other ITAM-associated myeloid cell receptors also require CARD9 and BCL10 for NF-κB activation [37, 38] (Fig. 2). In addition, Dectin-1 can also activate the NF-κB pathway via the kinase RAF1 in a SYK-independent manner [39].

The crucial roles of Dectin-1 and CARD9 in antifungal immunity have been demonstrated in mice as well as in humans [32, 40]. In this respect, deletion of Dectin-1 results in increased susceptibility to systemic infection with *C. albicans* due to impaired inflammatory responses in macrophages and reduced fungal killing by neutrophils [40, 41]. Likewise, CARD9-deficient mice are also highly susceptible to *C. albicans* infection due to impaired pro-inflammatory responses [32]. Subsequent human genetic studies have recognized loss of function mutations in Dectin-1 or CARD9, caused by either an early-stop-codon mutation (Tyr238X) in Dectin-1 or a premature termination codon (Q295X) in CARD9 in families suffering from chronic mucocutaneous candidiasis [42, 43]. Together, the human and mouse genetic data revealed that the Dectin-1/Syk/CARD9 pathway is an innate signaling pathway, that is important for antifungal responses. Importantly, triggering of this pathway in DCs can also activate adaptive immunity and induce strong Th17 immune responses which are vital for antifungal defense [33].

Dectin-2 is a second SYK-coupled CLR that controls antifungal immunity. Dectin-2 is also expressed on myeloid cells, B cells and neutrophils [31]. The extracellular CTL domain can bind to *C. albicans* and other fungi and has specificity for high-mannose structures [44]. In contrast to Dectin-1, however, Dectin-2 does not contain an intracellular signaling tail but rather associates with the ITAM-containing adaptor molecules Fc receptor γ chain (FcRγ) [28, 45] to initiate cell activation. Ligand binding to Dectin-2 (for instance upon *C. albicans* recognition) triggers phosphorylation of the FcRγ ITAM, recruitment of SYK and engagement of CARD9 for pro-inflammatory responses [28]. Similar to Dectin-1 ligation, activation of SYK / CARD9 signaling via Dectin-2 activates Th-17 T cell responses [28].

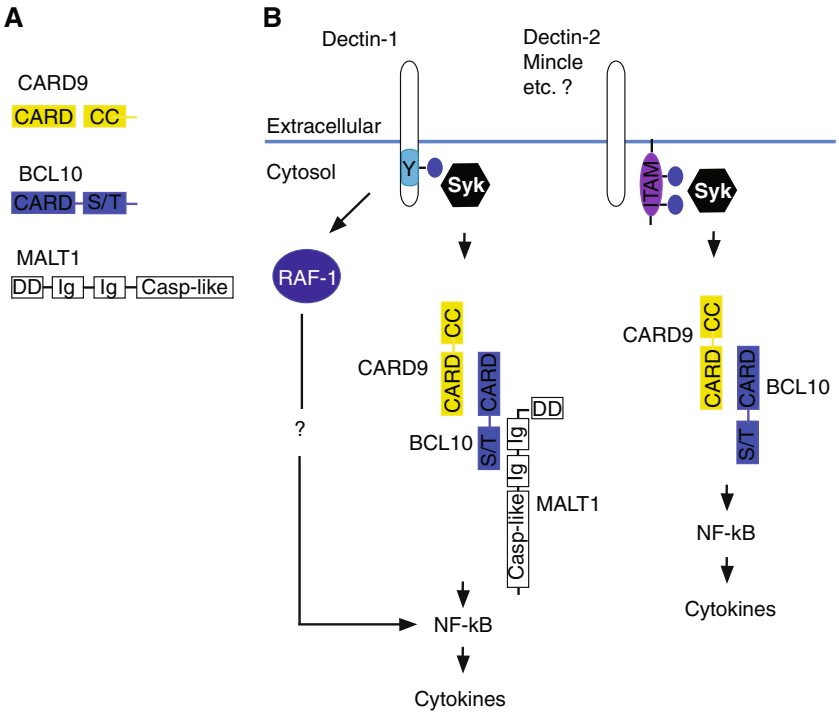

Fig. 2 ITAM receptors and CARD9 signaling. (**A**) Domain organization of CARD9, BCL10 and MALT1. CARD9 contains a caspase recruitment domain (*CARD*) and a coiled-coil domain. BCL10 contains a CARD that can interact with the CARD of CARD9. In addition, BCL10 possesses a serine and threonine (S/T)-rich region. The paracapsase MALT1 is composed of a death domain (DD) and immunoglobulin repeats (Ig) that mediate protein—protein interactions and contains in addition a proteolyticly active domain that resembles the catalytic region of Caspases (Casp-like). (**B**) Recognition of fungi by DC-associated C-type lectin 1 (Dectin-1) induces phosphorylation of the intracellular signaling tail with an atypical immunoreceptor tyrosine-based activation motif (ITAM, Y) and subsequently spleen tyrosine kinase (*SYK*) is recruited. Dectin-2 or Mincle and potentially other CLRs pair with ITAM-containing adaptor proteins to recruit SYK for further signal propagation. Via so far unknown mechanisms a complex is formed containing CARD9 (caspase recruitment domain family, member 9) and B cell lymphoma 10 (*BCL10*). This results in activation of nuclear factor-kappaB (*NF-κB*), which then induces the transcription of proinflammatory cytokines such as IL-6, TNF-α or pro-IL-1β. In addition, Dectin-1 can also activate the NF-κB pathway via the kinase RAF-1 in a SYK-independent manner. For details see text

Mincle is a third myeloid CLR that is able to recognize *C. albicans* and other fungi and induces inflammatory signals [30]. Mincle is predominantly expressed on myeloid cells [31]. Mincle can detect α-mannosyl expressed by pathogenic fungi like *Malassezia* spp. and glycolipids (trehalose-6,6′-dimycolat (TDM)) present in the cell wall of mycobacteria (such as *M. tuberculosis*). Thus, Mincle may be able to recognize unique fungal and bacterial structures such as glycolipids to initiate antibacterial and antifungal immunity.

Both SYK and CARD9 fulfill non-redundant roles in the activation of pro-inflammatory responses including synthesis of pro-IL-1β [9]. Thus, the SYK / CARD9 axis is key for the first signal of fungus induced IL-1β production. In addition, SYK kinase activity is also required for inflammasome activation and pro-IL-1β cleavage (signal 2) upon fungal infection [9].

Fungi Trigger Syk-Dependent NLRP3 Inflammasome Activation

As indicated above, the NLRP3 inflammasome is indispensable for IL-1β production induced by fungi. Mice that are deficient for the additional NLRP3 inflammasome components ASC or Caspase-1 all have defects in Caspase-1 activation or IL-1β production upon fungal recognition [9]. Moreover, Nlrp3-deficient mice are highly susceptible to systemic *C. albicans* infection [9–11], as it has been known for some time that IL-1β is critical for host defense against disseminated candidiasis [25, 46]. One study reported a particular relevant mouse model of sustained mucosal *C. albicans* colonization that resembles the clinical situation in human patients observing impaired survival and increased fungal titers in the tongues of Nlrp3-deficient mice [10].

The precise molecular details for fungus-induced NLRP3 activation are still not resolved. Yet, several common mechanisms for NLRP3 activation have been identified in other settings. The common triggers of NLRP3 activation include potassium efflux [47], lysosomal disruption [13, 22] and the generation of ROS [12] which may directly be sensed by NLRP3 or alternatively, oxidize a cellular factor that binds to and indirectly activates NLRP3. A recent report shows that treatment with NLRP3 agonists drives the association of NLRP3 with thioredoxin-interacting protein (TXNIP; also known as VDUP1) in a ROS-dependent manner [48, 49]. Finally, full activation of the NLRP3 inflammasome often requires a so called "priming" signal for example through a PRR such as TLRs or NLRs for NF-κB-dependent transcriptional upregulation of NLRP3 [50].

Experiments with ROS scavengers have indicated important roles for ROS production in *C. albicans*-induced inflammasome activation [9]. Moreover, *C. albicans*-triggered NLRP3 activation requires potassium efflux [9], but not lysosomal disruption [9] suggesting that *C. albicans*-induced inflammasome activation can be independent of the lysosomal pathway.

Intriguingly, NLRP3 inflammasome activation by *C. albicans* requires in addition to ROS production and potassium efflux also SYK kinase activity (Fig. 3). SYK deficient dendritic cells or cells that were pretreated with a

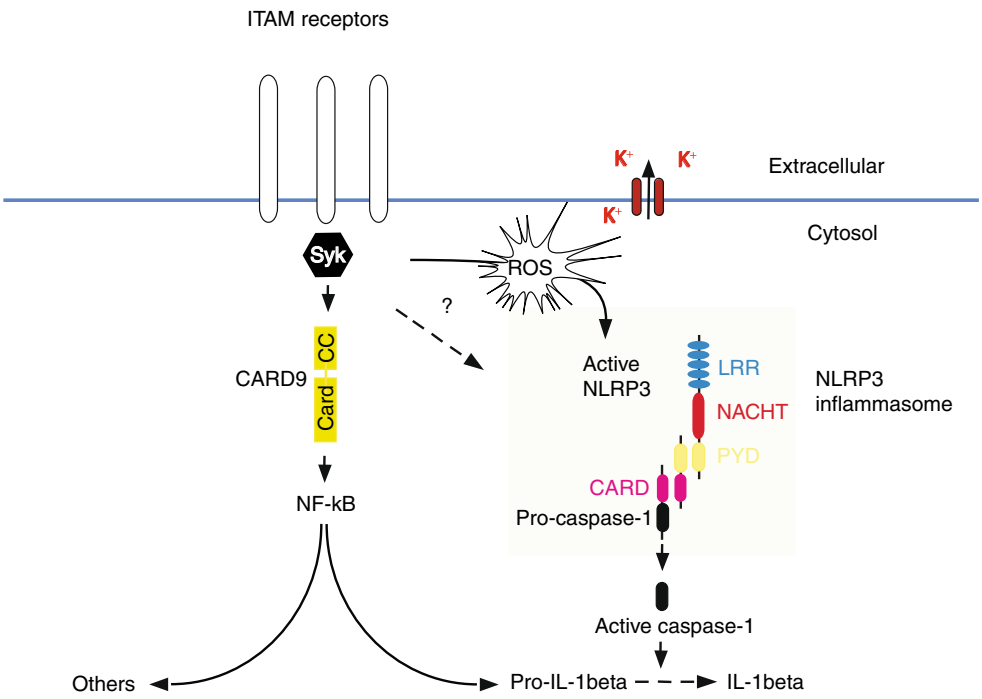

Fig. 3 SYK-dependent NLRP3 inflammasome activation by fungi. *Candida albicans* induces the synthesis of pro-interleukin-1β (pro-IL-1β) via SYK and CARD9-dependent pathways. *Candida albicans* can also activate the NLRP3 inflammasome through a mechanism that involves SYK-dependent generation of reactive-oxygen species (*ROS*) and potassium efflux. C-type lectin receptors (*CLRs*) that recognize fungi are presumably activating SYK for pro-IL-1β production and NLRP3 activation. In addition, still uncharacterized factors ("?") from viable yeast are required to cooperate with SYK signaling for NLRP3 activation. For details see text

small molecule SYK kinase inhibitor do not produce IL-1β upon fungal infection [9, 51]. This failure is not only caused by defective upregulation of pro-IL1β—which involves the SYK / CARD9 pathway—but also by a failure of Caspase-1 activation. In contrast, CARD9 deficient cells, which also have defects in *C. albicans*-induced IL-1β production (due to defective pro-IL-1β synthesis) show regular *C. albicans*-induced Caspase-1 activation after prestimulation with LPS [9]. Thus, the failure of SYK deficient cells to activate NLRP3 is not simply due to a defect in SYK/CARD9-dependent NF-κB signaling.

As indicated above, SYK signaling upon fungal recognition triggers ROS production [34] and inhibition of SYK with a kinase inhibitor reduces ROS synthesis [9]. Moreover, ROS inhibition with ROS scavengers block *C. albicans*-induced Caspase-1 activation. Thus, SYK-induced ROS synthesis seems to be a prerequisite for *C. albicans* induced NLRP3 activation. In addition, SYK signaling might also be essential for full transcriptional upregulation of NLRP3 or other factors that are required for inflammasome activation. In this context, it is important to note that SYK triggering by itself is not sufficient for inflammasome activation. Furthermore, it is still unclear how much the Dectin-1 / SYK signaling axis actually contributes to ROS upon fungal infection in vivo. However, cell treatment with fungal β-glucan preparations (zymosan) to engage Dectin-1 /SYK signaling [29, 33] does not activate NLPR3 at least by using shorter stimulation time points (e.g. 2–6 h after stimulation) [11, 52] [51] (and our own unpublished observations). Moreover, only viable but not heat-killed or UV-inactivated yeast cells activate NLPR3 [10, 11] and the transition from the yeast to the filamentous phase is important for this effect. Thus, additional still unidentified factors from viable yeast are required to cooperate with SYK for NLRP3 activation. The identification of these factors and signaling pathways will be an important step in further defining innate antifungal immunity and NLRP3 biology.

Conclusion

SYK-coupled CLRs are emerging as important activators of inflammatory responses, and can detect exogenous or endogenous ligands [31]. Furthermore, work over the last year has shed new light on ITAM receptor signaling, SYK and the NLRP3 inflammasome as key regulators of antifungal immunity [10, 11, 43, 52]. The identification of a cross talk between SYK and NLRP3 might have broader implications. Pro-inflammatory crystals such as uric acid particles which are responsible for NLRP3-dependent gout [14], activate SYK by direct lipid membrane binding [53]. Moreover, a recent study reported SYK-dependent NLRP3 inflammasome activation by malarial hemozoin [54]. Therefore, it is tempting to speculate that ITAM receptors and SYK might more commonly cooperate with NLRP3 inflammasome activation. In the future, it will be interesting to investigate a potential cooperation of ITAM receptors, SYK signaling and NLRP3 activation in inflammatory conditions.

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