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The interaction of *Candida albicans* with C-type lectin receptors

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Highlights

- Candidiasis is a substantial cause of perioperative mortality in immunocompromised and immunodeficient patients.
- β-glucan and α-mannan are two major pathogen-associated molecular patterns in the *Candida albicans* cell walls recognized by C-type lectin receptors (CLRs).
- CLRs, such as Dectin-1 and Dectin-2, as β-glucan and α-mannan receptors, are essentially involved in recogni tion of *Candida albicans*.
- CLRs are promising drug targets for treating chronic candidiasis.

Abstract

Candida albicans (*C. albicans*) is a ubiquitous commensal in the mammalian flora and the most prevalent fungal pathogen of humans. As an opportunistic fungus, *C. albicans* can cause mucosal and invasive infections. Invasive candidiasis infected by *C. albicans* is a leading cause of perioperative death in immunocompromised and immunodeficient patients. The morphological change from the yeast to the mycelium plays a key role in the pathogenesis of *C. albicans*. C-type lectin receptors (CLRs), including Dectin-1, Dectin-2, Dectin-3, Mincle, and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, are among the pattern recognition receptors expressed by innate immune cells that can recognize *C. albicans*. The emergence of drug-resistant *C. albicans* put pressure on the healthcare system, whereby CLRs have also attracted extensive attention from physicians. Thus, in this article, we discuss the interaction between CLRs and *C. albicans* and the treatment prospects of CLRs on anti-*C. albicans*.

Keywords: *Candida albicans*, virulence, C-type lectin receptors, anti-fungal immunity

Introduction

Candida species (*Candida* spp.) are common commensals in the skin and gut microbiota, colonizing the skin and mucosal surfaces of healthy individuals. *Candida albicans* (*C. albicans*) is the most common *Candida* spp. in clinic and one of the major causes of hospital-acquired infections. *C. albicans* is responsible for more than 400,000 invasive candidiasis cases annually with a high mortality rate of 75% [1, 2]. In healthy humans, *C. albicans* is usually harmless. However, they can be hyperproliferative, leading to invasive *Candida* infections in individuals, due to pH changes, nutrition, illness, and immune system disorders from the use of antibiotics and immunosuppressive agents [3]. Intensive care unit (ICU) patients usually have chronic underlying diseases with low immunity and disordered pathophysiological conditions [4]. In the last two decades, there is an increase in fungal isolates from ICU subjects due to improvements in diagnostics, overuse of antibiotics, and better organ support systems prolonging ICU stay [5]. In a report from eastern India, *Candida* spp. were detected in nearly 15% of isolates [6]. Perioperative medicine is a subject of multidisciplinary perioperative

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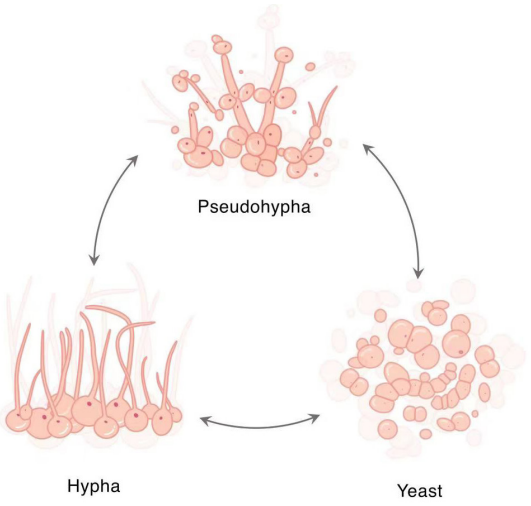

Figure 1. Phenotypic switching in *C. albicans*. *C. albicans* can switch among yeast, hypha, and pseudohypha cell types, depending on the environmental and nutritional factors. *C. albicans, Candida albicans.*

management, which is centered on surgical patients, based on value medicine, and aimed to promote the high quality of postoperative recovery of patients [7]. Surgical treatments play important roles in curing diseases. With the update of ideas and the progress of technology, clinicians gradually realize that the focus of disease treatment is not only the operation itself but also the preoperative and postoperative treatment. After some surgeries like cancer surgery, patients may require ICU admission for postoperative therapy [8]. However, ICU settings are conducive to *C. albicans* infection [9]. It has become increasingly challenging for clinicians to manage the *C. albicans* in ICUs, which was recently found in 52% of the observed cases in ICU [10, 11]. *C. albicans* is the most frequent isolate in yeast-positive cultures in patients with sepsis, and the mortality rate can reach 80% in patients with candidemia if no treatment is received within the first 24 h of septic shock [12].

In recent years, the annual incidence of invasive candidiasis has increased due to the widespread use of broad-spectrum antibiotics, glucocorticoids, and immunosuppressive agents. *C. albicans* infection is particularly severe in immunocompromised patients, such as those with acquired immunodeficiency syndrome, those receiving chemotherapy and immunosuppressive agents, and those implanted with medical devices. Virulence factors for *C. albicans* allow it to adhere to and penetrate host tissues, resulting in local diseases such as oral candidiasis, onychomycosis, and vaginitis. *C. albicans* have a strong morphological plasticity and can grow in yeast, pseudohyphae, or hyphae, and this polymorphism is strongly associated with its pathogenicity [13]. Additionally, biofilm formation is also one of the important virulence factors for this microorganism.

Pathogen-associated molecular patterns (PAMPs) exist on the surface of various pathogenic microorganisms. They exhibit unique characteristics specific to certain microorganisms, possess constant structural features, and demonstrate evolutionary conservation. Mainly expressed on the surface, cytosol, and serum of innate immune cells (macrophages, dendritic cells, etc.), pattern recognition receptors (PRRs) directly recognize pathogen surfaces such as the fungal cell wall components mannose, chitosan and β-glucans. Common PRRs include toll-like receptors (TLRs), nucleoside receptors (NLRs), retinoic acid-inducible gene I-like receptors, and C-type lectin receptors (CLRs) [14]. In recent years, CLRs play a pivotal role in host antifungals especially *anti-C. albicans* infection, which has attracted increasing attention. The interactions between CLRs and *C. albicans,* as well as their role in the induction of protective immunity, is elaborated in this study. The main CLRs involved in the recognition of *C. albicans* include Dectin-1 (*CLEC7A*), Dectin-2 (CLEC6A), Mincle (CLEC4E), DC-SIGN (CD209), and MCL / Dectin-3 (CLEC4D).

Virulence of *C. albicans*

Fungal cell walls are highly dynamic complex structures that play a role in maintaining cell shape and protecting cells. The robustness of the cell wall is the key to the maintenance of fungal morphology. Fungal cell walls are composed of rich composition of an inner layer of β-glucans and underlying chitin and an outer layer of mannosylated proteins. β-glucan is the major PAMP in the fungal cell walls and is cleared after recognition by the innate immune system [15]. Under normal conditions, *C. albicans* can mask the inner wall of cells by coating it with an outer layer of mannosylated protein β-glucans, which reduces the recognition of *C. albicans* by innate immune cells, enhancing their viability [16-18]. It has also been reported that the pathway for the synthesis of phosphatidylserine plays an important role in the masking of β-glucans [19]. *C. albicans* infection of macrophages triggers macrophage death, which is largely attributed to RIPK3/mixed linear kinase domain-like protein (MLKL)-mediated necroptosis. The TSC1/mTOR pathway is involved in regulating Dectin-1/2 and TLR-2/4 pathways, respectively, by binding fungal

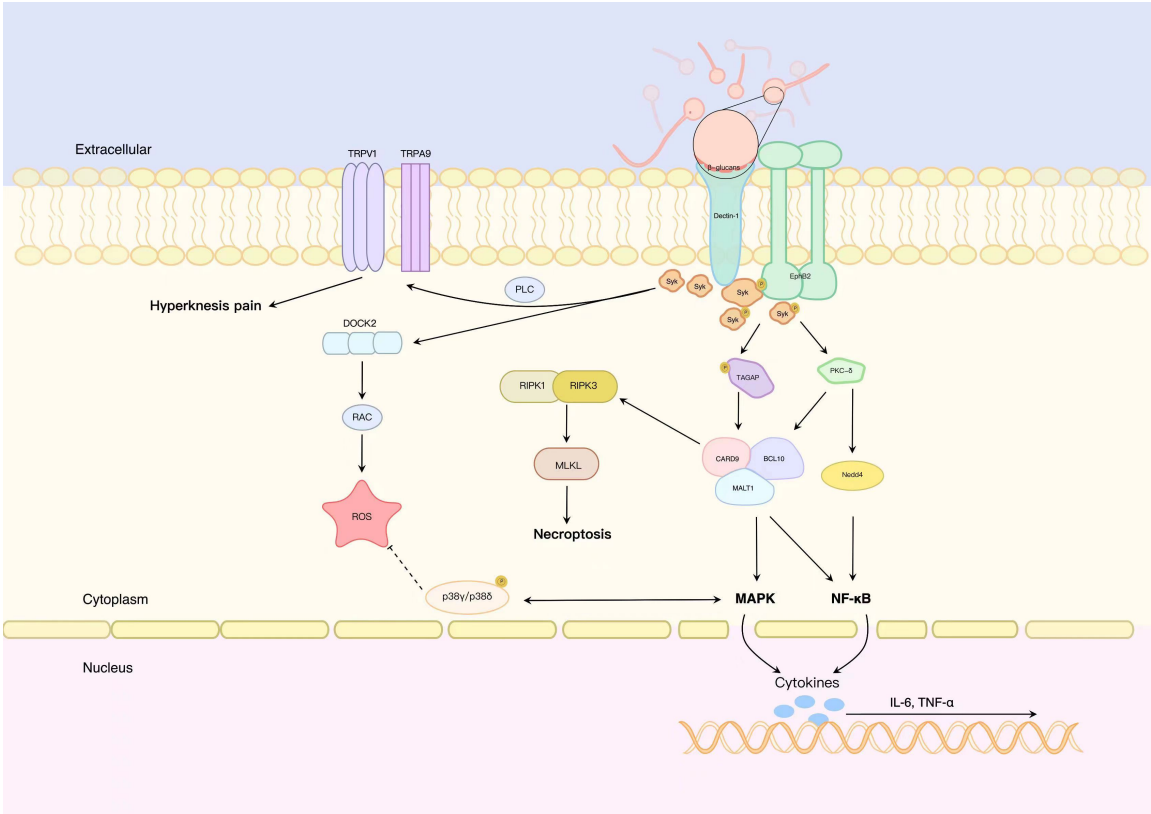

Figure 2. Dectin-1 against *C. albicans*. The recognition of ligands by Dectin-1 triggers SYK recruitment and downstream intracellular signaling. EphB2 is required for SYK phosphorylation and activation following Dectin-1 ligand stimulation. TAGAP is tyrosine phosphorylated by the EphB2 gene, which links dectin-1-induced EphB2 activity to downstream CARD9-mediated signaling pathways. PKC δ is activated upon Dectin-1-SYK signaling, which mediates phosphorylation of CARD9, and favors CARD9-BCL10-MALT1 complex formation and activation of NF- κB. The ubiquitin ligase Nedd4 is located in PKC-δ downstream, which is critical for signaling through Dectin-1 and the activation of NF-κB. Necroptosis is a newly discovered type of programmed cell death. It activates the actuator MLKL through the specific signal cascade of RIPK1 and RIPK3 complex. p38γ/p38δ deficiency protects against *C. albicans* infection by increasing the production of reactive oxygen species. DOCK2 is a nucleotide exchange factor for RAC. Fungus-induced ROS production is partially dependent on the DOCK2-RAC GTPase pathway. In addition, β-glucan can stimulate Dectin-1-dependent nociceptors, which causes unpleasant sensations. *C. albicans*, *Candida albicans*; TAGAP, T cell activation Rho GTPase activating protein; EphB2, Eph receptor B2; CARD9, caspase recruitment domain-containing protein 9; PKC, Protein kinase C; SYK, spleen tyrosine kinase; NF-κB, nuclear factor-κB; MLKL, mixed linear kinase domain-like protein; RIPK, receptor interaction protein kinase; DOCK2, dedicator of cytokinesis 2; ROS, reactive oxygen species.

component β-glucan or α-mannan. The pathway also plays a key role in controlling macrophage necroptosis [20].

C. albicans is a polymorphic fungus that can grow in yeast or hyphal forms, and its ability to interconvert between these forms is considered an important virulence trait (**Figure 1**) [21]. When the flora is dysregulated or the mucosal barrier function is altered, *C. albicans* switches from a yeast state to a mycelial state, releases secretory proteins, invades and colonizes host cells, thus destroying host cells. Yeast wall protein 1 is an abundant mannoprotein of the yeast cell wall. When anchored in the cell wall, yeast wall protein 1 has an anti-adhesive and masking effect, leading to β-glucan unexposed, reducing the adhesivity of *C. albicans*, and protecting *C. albicans* from recognition by the immune system [22]. *UME6* is a transcriptional regulator of *C. albicans* hyphae and is essential for systemic Th17 immunity triggered by intestinal *C. albicans*. Studies have demonstrated a greater ability of hyphal *C. albicans* to invade the host than in the yeast state. Once hyphae are formed, their associated virulence factors are abundantly expressed, thus increasing the pathogenicity of *C. albicans* [23].

C. albicans exotoxin candidalysin is the first peptide toxin secreted by hyphae of *C. albicans* found in human pathogenic fungi [24]. Candidalysin is encoded by the *C. albicans* gene *ECE1*, which is one of the most expressed genes during the formation of mycelial. The expression of *ECE1* can increase to 10,000 times within a few minutes after the induction of mycelial growth [25]. When *C. albicans* are engulfed by macrophages, the expression of the *ECE1* gene encoding *C. albicans* is significantly enhanced. Therefore, mature *C. albicans* may be produced by *C. albicans* cells engulfed

by macrophages and play a toxin-dependent effect [26]. Candidalysin has dual functions in the interaction with the host. On the one hand, candidalysin can promote the damage to the host cell membrane, which is related to escape from phagocytes. On the other hand, it can activate NLRP3 inflammatory corpuscles and trigger a pro-inflammatory reaction that protects the host, which is beneficial to the elimination of fungus [26, 27]. In addition, Candidalysin can destroy primary hepatocytes in a dose-dependent manner in vitro [28]. It can promote alcohol-induced liver disease and is positively correlated with the severity of liver disease and mortality of patients with alcoholic hepatitis.

CLRs and *C. albicans*

Dectin-1

Dectin-1 is a type II transmembrane receptor with a single extracellular C-type lectin-like domain encoded by the *CLEC7A* gene [29-31]. It is mainly expressed by myeloid cells (e.g., neutrophils, monocytes, and dendritic cells) and is the major CLR that recognizes β-glucans in fungal cell walls (**Figure 2**) [32-34]. The recognition of its ligands by Dectin-1 triggers complex downstream signaling pathways with interconnected relationships [31]. Spleen tyrosine kinase (SYK) is a cytoplasmic nonreceptor protein tyrosine kinase that plays an important role in oxidative response and bactericidal activity. Dectin-1 is essential for SYK recruitment and triggers intracellular signaling [35, 36].

It is generally believed that DOCK2, a member of the CDM protein family, is an upstream molecule of RAC and functions as a guanine nucleotide exchange factor for RAC. Recently, Ma et al. found that in DOCK2-KO THP-1 cells, reactive oxygen species (ROS) production was severely impaired, but after treatment with RAC GTPase inhibitors, ROS production was not completely blocked [37]. This indicates that fungal-induced ROS production is partially dependent on the DOCK2-RAC GTPase pathway, and there is a RAC GTPase-independent and Dock2-dependent mechanism for ROS production. Protein kinase C-δ (PKC-δ) is activated upon Dectin-1-SYK signaling, mediates phosphorylation of CARD9, and favors CARD9-BCL10-MALT1 complex formation and activation of NF- κB [36, 38].

The tyrosine kinase receptor Eph receptor B2 (EphB2), a kinase of SYK, was recently shown to be required for SYK phosphorylation and activation following Dectin-1 ligand stimulation [39]. It has also been shown that SYK can promote phosphorylation of EphB2, and co-expression of SYK significantly facilitates the interaction between Dectin-1 and EphB2. T cell activation Rho GTPase activating protein (TAGAP) is essential in Dectin-1-induced antifungal signaling and proinflammatory cytokine production by myeloid cells. Upon stimulation by Dectin-1 ligands, EphB2 was phosphorylated by SYK and further phosphorylates TAGAP, which links Dectin-1-induced EphB2 activity to downstream CARD9-mediated signaling pathways. During *C. albicans* infection, mice lacking TAGAP can develop defective immune responses, impaired Th17 cell differentiation, and a higher fungal burden [40]. The ubiquitin ligase Nedd4 is located in PKC-δ downstream and plays a crucial role in signaling through Dectin-1, as well as in the activation of NF-κB [41].

Dectin-1 is regulated by multiple factors. miR-155, as a multifunctional microRNA (miRNA), is a key regulator of innate immune responses against bacteria and viruses. The Dectin-1 pathway can be activated by NF-κB, p65, and Bcl-10, promote the expression of miR-155 in SYK-dependent manner, and reduce the excessive inflammation caused by *C. albicans* [42, 43]. Overexpression of granulocyte-macrophage colony-stimulating factor (GM-CSF) is a dependent feature of β-glucan-induced macrophage priming. GM-CSF can upregulate Dectin-1 expression. However, a study found that blockade of the GM-CSF pathway did not affect levels of β-glucan, suggesting that GM-CSF is not acting primarily on β-glucan [44]. Song et al. recently found the activation of mast cells and the overexpression of Dectin-1 in patients with *C. albicans* infection, which promoted the activation of downstream MAPK signal pathway [45]. The deletion of CD82 could regulate Dectin-1 signal transduction, resulting in the reduction of SYK phosphorylation and the production of ROS in response to *C. albicans* infection [46]. Lactobacillus down-regulated the transcription of *CLEC7A*, resulting in a decrease in the expression of Dectin-1. Lactobacillus changed the cytokine profile of macrophages stimulated by *C. albicans*, increasing the expression of IL-10 and IL-1β and decreasing the expression of IL-12. These results indicate that lactobacillus can damage the recognition of PAMP by macrophages and regulating inflammation [47]. The autoimmune regulatory gene (*AIRE*) can also regulate the SYK-dependent Dectin-1 pathway. *AIRE*-knockdown macrophage-like THP-1 cells showed down-regulation of Dectin-1 and Dectin-2 receptors, and reduction in activity of hyphal recognition, phagocytosis of C. albi-

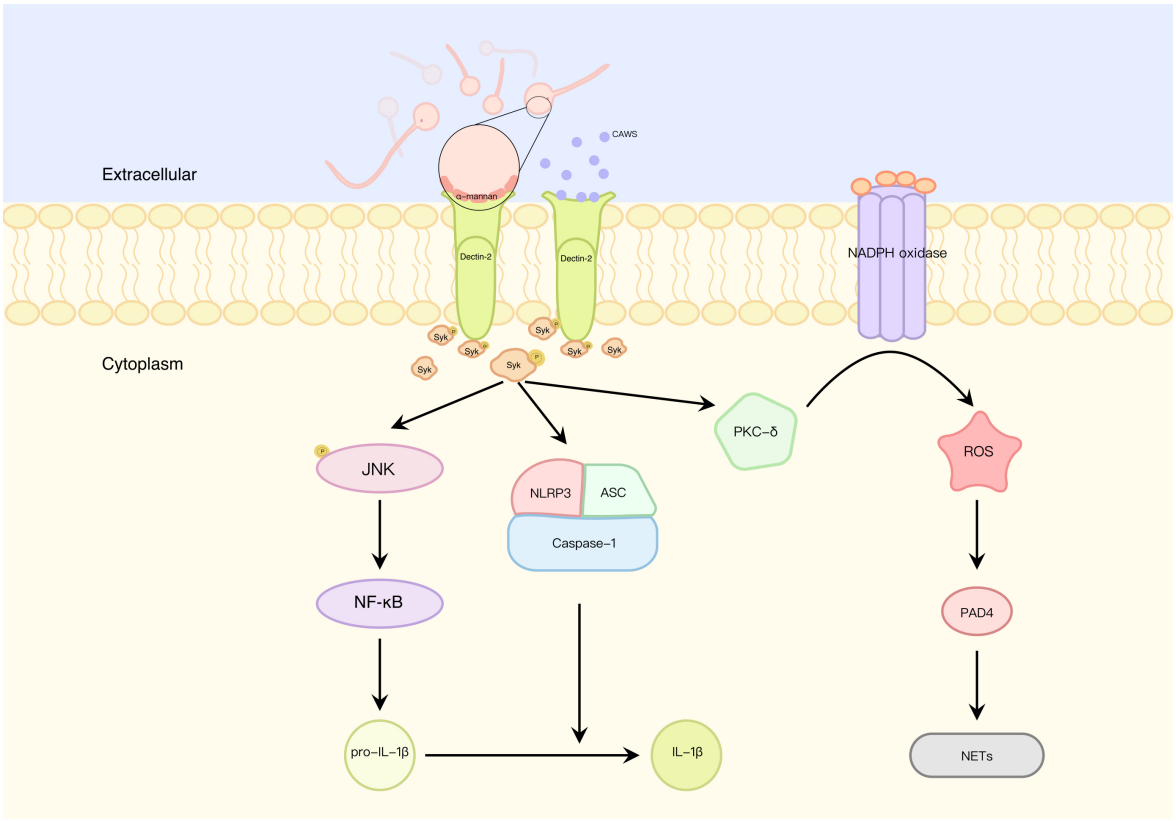

Figure 3. Dectin-2 against *C. albicans*. Dectin-2 can recognize α-mannan in the fungal cell wall. After α-mannan is recognized by Dectin-2, it can also send signals through CARD9, causing the activation of NF-κB. Dectin-2 can activate the downstream SYK-Ca^{2+}-PKC δ PAD4 signal pathway, mediate the production of NADPH oxidase independent NETs, and contribute to the production of ROS. CAWS can induce NLRP3 and pro-IL-1β expression via Dectin-2/SYK/JNK/NF-κB pathways and activate Dectin-2 as well as cleavesIL-1β precursor via caspase-1/SYK/JNK mediated production of ROS. *C. albicans*, Candida *albicans*; PAD4, protein arginine deiminase 4; CARD9, caspase recruitment domain-containing protein 9; NF-κB, nuclear factor-κB; SYK, spleen tyrosine kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NETs, neutrophil extracellular traps; IL, interleukin; ROS, reactive oxygen species.

cans, and formation of lysosomes. Besides, the expression of IL-1β, IL-6, and TNF-α were also reduced [48].

The insolubility of the cell wall of *C. albicans* β-glucan can increase the generation of IL-6 and TNF-α by Dectin-1-SYK-NF-κB and p38 MAPK pathways [49]. Dectin-1 recognizes β-glucan by activating PKC-δ and regulates glucose transporter 1 (GLUT1) phosphorylation, localization, and early glucose transport in neutrophils. The host response to disseminated candidiasis involves renal immunity, modulation of GLUT1 expression, and localization. This increases neutrophil glycolytic activity and upregulates glucose uptake [50]. Necroptosis is a newly discovered type of programmed cell death. It activates the actuator MLKL through the specific signal cascade of receptor interaction protein 1 (RIPK1) and RIPK3 complex. Fungi trigger the necrotic apoptosis of myeloid cells, which helps the host defense against pathogen infection. The activation of *C. albicans* and its sensor Dectin-1 induces necroptosis of myeloid cells through the RIPK1-RIPK3-MLKL pathway. CARD9 is a key adapter of Dectin-1 signal transduction and is identified as a link between RIPK1 and RIPK3 complex-mediated necroptosis pathway. RIPK1 and RIPK3 also enhance the MLKL-independent inflammatory response induced by Dectin-1. Both MLKL-dependent and MLKL-independent pathways are necessary for host defense against *C. albicans* infection [51].

In addition, β-glucan can stimulate Dectin-1-dependent nociceptors, as well as pathways of inflammatory pain. The major pathway acts through a Dectin-1-mediated ATP-P2X3/P2X2/3 axis via the intercellular relationship between keratinocytes and primary sensory neurons, which depends on the ATP transporter vesicular nucleotide transporter (VNUT). Another pathway works through a Dectin-1-mediated PLC-TRPV1/TRPA1 axis in primary sensory neurons. Interestingly, in the cell wall of *C. albicans*, β-glucan can enhance histamine-dependent itching, and the VNUT inhibitor clodronate can be used to treat itch induced by β-glucan-induced unpleas-

ant sensations (**Figure 2**) [52]. β-glucan was masked at low oxygen level, which hinders the PAMP sensing of Dectin-1 on the surface of polymorphonuclear leukocytes. This in turn contributes to the immune escape and improves the survival rate of fungus [53]. Homologous phosphatases Sts protein negatively regulates phagocyte activation by regulating selective elements of the Dectin-1-SYK tyrosine kinase signaling axis, and genetic inactivation of Sts significantly improves the survival of mice infected with *C. albicans*, which may facilitate the development of novel therapeutic approaches to enhance protection against invasive candidiasis [54].

C. albicans, through the β-glucan receptor Dectin-1, stimulates nav1.8-positive nociceptors, inducing calcitonin gene-related peptide (CGRP). CGRP can directly inhibit P65 through transcriptional repressor JDP2, thereby inhibiting β-glucan-induced inflammation and osteoclast multinucleation, indicating a role for the Dectin-1-mediated sensory secretion pathway in the resolution of fungal bone inflammation [55]. Taurochlorolamine (TauCl), formed by the reaction between taurine and hypochlorite in leukocytes, is especially abundant in activated neutrophils with an oxidative burst. As neutrophils undergo apoptosis, TauCl is released into the extracellular matrix at the site of inflammation, thereby affecting coexisting macrophages in the inflammatory microenvironment. Exogenous TauCl can significantly increase the phagocytic efficiency of macrophages by upregulating Dectin-1. This may be mediated by TauCl induction of heme oxygenase-1 expression and subsequent production of carbon monoxide. TauCl has an important role in host defense against fungal infections and has a therapeutic potential in the management of inflammatory diseases [56].

Recently, a new TAK1-TPL2-MKK1-ERK1/2 pathway was found in macrophages. It is considered to be activated by Dectin-1 and positively regulated by p38γ/ p38δ in bone marrow cells. In mice, p38γ/p38δ deficiency has a protective effect against *C. albicans* infection. This protection is achieved through increased production of ROS, which enhances the antifungal capacity of macrophages. Additionally, p38γ/ p38δ deficiency helps in reducing excessive inflammation, which can lead to severe damage to the host. In murine models, pharmacological inhibition of p38 MAPK was shown to reduce the fungal burden, suggesting that p38 MAPK may be a therapeutic target for the treatment of human *C. albicans* infections [57]. Furthermore, β-glucan triggers the production of neutrophil extracellular trap nets through Dectin-1 and the engagement of CD11b and CD18 receptors, which is a fascinating antifungal mechanism for neutrophils [58].

Dectin-2

Dectin-2 (CLEC6A) is a CLR that mainly exists in dendritic cells, macrophages, and neutrophils. Dectin-2 has been proven to recognize α-Mannan in the fungal cell walls (**Figure 3**) [59, 60]. After α-mannan is recognized by Dectin-2, it can also send signals through CARD9, causing the activation of NF-κB, and inducing the production of inflammatory cytokines [61]. Dectin-2 can activate the downstream SYK-Ca^{2+}-PKC-δ protein arginine deiminase 4 (PAD4) signal pathway, mediate the production of NADPH oxidase independent neutrophil extracellular traps (NETs), and contribute to the inhibition of fungal dissemination [62]. Dectin-2 has been shown to mediate phagocytosis, cytokine, and ROS production. In *C. albicans* infection, it promotes IL-12p40, IL-1β, and IL-23 production by dendritic cells (DCs) to induce the generation of protective Th1 and Th17 responses [63]. Also, Dectin-2-deficient mice were shown to have a poor capacity to secrete Th1 and Th17 cytokines to generate ROS [64].

Recently, it has been shown that the recognition of α-mannans by Dectin-2 is a key to the pathogenesis of Kawasaki disease (KD)-like vasculitis induced by cell wall of polysaccharide of *C. albicans* in mice [65]. In a study of a *C. albicans* water-soluble fraction (CAWS)-induced murine KD model, it was found that the NLRP3 inflammasome was required for the development of CAWS-induced vasculitis and that Dectin-2 signaling in macrophages in the aortic root of the heart induced early CCL2 production, which in turn induced vascular inflammation [66]. CAWS triggers Dectin-2/SYK/JNK/NF-κB pathways, leading to the induction of NLRP3 and pro-IL-1β expression. It also activates Dectin-2 as well as cleaves IL-1β precursor via caspase-1/SYK/JNK mediated production of ROS [67, 68]. These findings provide new insights into the pathogenesis of KD vasculitis, and suggest that NLRP3 inflammasome may be a potential therapeutic target for KD.

Dectin-3

Dectin-3 (CLEC4D), which can be expressed by multiple myeloid cells, is a myeloid cell-specific CLR family member that can recognize bacterial and fungal components and induce

intracellular signaling pathways to regulate immune responses[69]. Dectin-3 recognizes the α-mannan on the surface of *C. albicans* and induces NF-κB activation [70]. Recently, it was found that Dectin-3 knockout (Dectin-$3^{-/-}$) mice exhibited increased tumorigenesis and *C. albicans* burden during chemical induction, indicating that Dectin-3 may be the key CLR to identify and prevent *C. albicans* [71]. In addition, the interaction between Dectin-3 and symbiotic fungi is indispensable for the homeostasis regulation of the intestinal immune system. Mice lacking Dectin-3 are more likely to suffer from colitis induced by dextran sulfate [72].

Mincle

Mincle (CLEC4E) is a CLR that is expressed in macrophages. Mincle binds to α-mannan that interferes with Dectin-1-mediated antifungal responses in human dendritic cells [73, 74]. Mincle receptor is an Fc receptor-γ coupled receptor that can transmit signals through SYK pathway [75]. It has been demonstrated that mincle regulates antifungal immune function by binding to ITAM connector molecule Fc receptor-γ, recognizing damaged cells and inducing inflammation [76]. Upon recognition of the ligand, mincle activates SYK and other downstream signaling cascades to induce inflammatory cytokines [77, 78]. In the absence of mincle, the TNF-α produced by macrophages is reduced, and mice lacking mincle exhibits a significantly increased susceptibility to systemic candidiasis. This indicates that the mincle receptor plays an important role in the immune process of organisms against *C. albicans* infection. Mincle has been shown to mediate the production of TNF-α by BMDMs in response to *C. albicans* [73]. Both mincle and Dectin-2 play a role in regulating cytokine production in response to multiple Candida spp. In BMDCs, mincle mediates IL-12p40 production and inhibits IL-1β production, whereas Dectin-2 promotes the production of IL-12p40 and IL-10, in response to multiple Candida spp [79].

Mincle receptors from different cells also seem to have varying effects. The expression of mincle on neutrophils seems to be beneficial to early cell response, leading to the elimination of organisms. However, its expression on monocytes may contribute to the polarization of cell reactions, avoiding clearance and promoting the generation of TNF-α, IL-1β [80]. Furthermore, mincle is required for *C. albicans* clearance in the kidney [73].

DC-SIGN

DC-SIGN (CD209) is another member of the CLR family that mainly found on the surface of immature DCs in peripheral tissues, mature DCs in lymphoid tissues, and some macrophage subsets [81]. DC signaling reduces TGF-β1 through the activation of Raf-1 and p38 [82]. DC-SIGN directly binds to glycan structures exposed on the surface of pathogens [79]. DC-SIGN directly binds to glycan structures exposed on the surface of *C. albicans*, activates the Raf-1-acetylation-dependent signaling pathway to increased IL10 transcription to enhance anti-inflammatory cytokine responses [83, 84].

CLRs in the treatment of *C. albicans*

In a recent study on GPI7 mutants of *C. albicans*, Dectin-1 was observed to signal through the recognition of GPI7 mutants on the cell surface β-1,3-glucan, leading to atypical NF-κB nuclear translocation. This regulates the production of IL-18 as well as major Candida antibodies. A2-aminonicotinamide derivative, 11G, which is revealed by β-glucan, activates Dectin-1-dependent protective immune responses and enhances fungal immunogenicity, is a very promising antifungal drug [85]. Morphological conversion between *C. albicans* yeast and hyphae is essential for its interaction with the defense system of the host, and the Flo8 gene may regulate this conversion process. Furthermore, Flo8 induces Dectin-2/CARD9 to mediate IL-10 production by DCs and macrophages, blocks thymic atrophy by suppressing *C. albicans*-induced apoptosis of thymic T cells, and promotes sustained export of naive T cells from the thymus to the spleen [86]. Dectin-2 is a drug target for controlling IL-10 production in vivo and treating chronic candidiasis.

Amphotericin liposomes coated with Dectin-2, specifically the mannan-binding domain of Dectin-2, exhibited enhanced binding to *C. albicans* than untargeted control liposomes, significantly reducing the effective dose. Further, amphotericin B-loaded Dectin-2-coated liposomes demonstrated 50 to 150 times stronger binding to *C. albicans*, compared to untargeted liposomes [87]. DectiSomes are a novel antifungal drug targeting technology [88]. Two types of DectiSomes, DEC1-AmB-LL and DEC2-AmB-LL, were developed by coating AmB-LL with the carbohydrate recognition domains of Dectin-1 and Dectin-2, respectively [89]. These targeted formulations demonstrated superior efficacy compared to non-targeted drugs in terms of fungal cell binding and killing, both in vitro and in vivo. Additionally, they effectively reduced the

burden of fungi in the kidney [90]. But for cryptococcus neoformans, Dectisomes may reduce antifungal activity. Moreover, with only moderate effects in penetrating the blood-brain barrier as well as significant cost, further efforts are required to make Dectisomes a clinical reality.

Ligand recognition by DC-SIGN is provided by a carbohydrate recognition domain (CRD) linked to membrane transport and signaling sequences, and different combinations of eight neck repeats (NR1 to NR8) expressed in different protein isoforms may alter the orientation of the CRD and the ability to bind to different polysaccharides. Two recombinant isomers were prepared and connected with lipid carriers to produce DCS12-AmB-LLs and DCS78-AmB-LLs. The liposome AmB was targeted to fungal cells with DC-SIGN. In the mouse model of invasive candidiasis and pulmonary aspergillosis, low-dose DCS12-AmB-LLs significantly reduced the fungal burden on the kidney and lung, which sheds light on future research in anti-*Candida* therapy [91].

In recent years, traditional Chinese medicine has been used to treat Candida infections. Sodium houttuyfonate is a promising anti-Candida traditional Chinese herbal medicine, which can induce β-glucan exposure, through the cooperation of Dectin-1 and TLR2/4, promotes intestinal macrophages to get rid of colonized *C. albicans*, reduces fungal load, and alleviates colitis associated with *C. albicans* [92]. Kangbainian lotion (KBN) is a Chinese plant preparation, which has achieved good clinical efficacy in the treatment of vulvovaginal candidiasis. It inhibits biofilm and hyphal formation, reduces adhesion, and inhibits ergosterol synthesis and the expression of ergosterol synthesis-related gene *ERG11*. KBN can also reduce the protein expression of inflammatory factors TNF-α, IL-1β, and IL-6 in vaginal tissue and inhibit the expression of proteins related to the Dectin-1 signal pathway [93]. Butyl alcohol extract of Baitouweng Decoction down-regulates key proteins in TLRs/MyD88 and Dectin-1/SYK signaling pathways, including ASC, caspase-1, Dectin-1, SYK, MyD88, TLR2, TLR4, and NF-κB, and exerts therapeutic effect in mice with vulvovaginal candidiasis [94, 95]. Paeonol can improve liver inflammatory injury by alleviating intestinal fungal flora imbalance and inhibiting fungal flora mediated Dectin-1/IL-1β signal pathway [96]. Cinnamaldehyde can reduce the content of TNF-α, IL-1β, IL-6, and IL-8 in serum and colon tissues, increase the content of IL-10, inhibit the infiltration of macrophages, and down-regulate the protein expression of Dectin-1, TLR2, TLR4 and NF-κB in colon tissues, showing a therapeutic effect on mice with ulcerative colitis [97].

Discussion

C. albicans are usually a benign member of human intestinal microflora, but in some cases, such as in the host with low immune function, the ecological imbalance of intestinal fungi can lead to invasive infection and inflammatory bowel disease [98, 99]. Intestinal epithelial cells (IECs) may recognize the activation of the Wnt pathway by *C. albicans* through Dectin-1, leading to the progression of colorectal cancer [96]. However, IEC recognition of *C. albicans* does not lead to any detectable secretion of pro-inflammatory cytokines [100, 101].

This review summarizes the major CLRs against *C. albicans* besides CD23 (CLEC4J), which is also a kind of CLR and a well-known B-cell surface marker. CD23 can sense the components of *C. albicans* in antifungal immunity and recognize the components of *C. albicans* or Aspergillus fumigatus in the cell wall α-mannan and β-glucan, but it cannot recognize the glutaraldehyde xylimanna in Cryptococcus. By interacting with the FCR-γ and forming a complex, CD23 can induce NF-κB activation [102]. However, it remains unclear how CD23 functions as a fungal PRR and whether the antifungal effect of CD23 is specific to *C. albicans*. Infection of macrophages with *C. albicans* can cause cell death, which is mainly due to RIPK3/MLKL-mediated necrotic apoptosis [20]. The size of *C. albicans* affects the phagocytosis of DCs, which prolongs the duration of Dectin-1 signal transduction, increases the expression of IL-33, and promotes the TH9 response [32]. Several microbial recognition receptors, including TLR2, MyD88, Dectin-1, Dectin-2, and the signaling molecule CARD9, are dispensable for host defense against *C. albicans* invasion in the epidermis. Instead, the production of IL-17A and IL-17F by innate lymphoid cells plays critical roles. Further studies are needed to understand how *C. albicans* is recognized in the superficial layers of the epidermis [103]. Besides, the coordinated action of CLRs plays a key role in effectively controlling *C. albicans* and preserving organ function during infection [104]. Dectin-2 and Dectin-3 form heterodimers to combine α-mannan more effectively, which leads to an effective inflammatory response against *C. albicans* infection. Dectin-1 signal activates RHOA pathway, leads to actin contraction, and promotes DC recruitment. Dectin-1 and DC-SIGN synergistically enhance the clear-

ance of *C. albicans* [70, 105].

Due to the long-term use of limited antibacterial drugs, the drug resistance of fungi is continuously increasing. However, the development of novel antibacterial drugs lags far behind the emergence of fungal resistance. Further studies of the mechanism of action between CLRs and *C. albicans* can provide new insights and strategies for the research of broad-spectrum antibacterial drugs, antitumor drugs, immunosuppressive agents, as well as the prevention and treatment of fungal infections caused by interventional surgery, organ transplantation, acquired immunodeficiency syndrome and so on.

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