The *Candida albicans* cell wall as a dynamic interface orchestrating environmental adaptation and pathogenesis

Youzhi Zhao[1], Wei Zou[1], Chang Su[2], and Yang Lu[1*]

[1]State Key Laboratory of Metabolism and Regulation in Complex Organisms, College of Life Sciences, TaiKang Center for Life and Medical Sciences, Wuhan University, Wuhan 430072, China;

[2]Hubei Key Laboratory of Cell Homeostasis, College of Life Sciences, Wuhan University, Wuhan 430072, China.

[*]Correspondence: ylu7@whu.edu.cn (Y.L.).

Abstract

In pathogenic fungi, the cell wall serves critical functions in sensing environmental cues, mediating signal transduction, and facilitating host-pathogen interactions. The cell wall of *Candida albicans*, one of the major pathogenic fungus of humans, comprises three primary structural components: β-glucans, chitin, and mannoproteins. Importantly, both polysaccharide and protein components undergo dynamic remodeling in response to environmental stresses and nutrient fluctuations within the host niche, enabling evasion or manipulation of innate immune surveillance. *C. albicans* also exhibits remarkable capacity for rapid and adaptive cell wall reprogramming to sustain survival when challenged with antifungal drugs. Notably, cell wall dynamics occur across other *Candida* species, albeit with distinct species-specific characteristics, as exemplified by *Candida auris*, a recently emerging fungal pathogen of significant clinical concern. This review summarizes current understanding of the mechanisms underlying fungal cell wall remodeling elicited by host signaling, a dynamic process that facilitates both survival and establishment of infection, using the human pathogen *C. albicans* as the principal model organism.

Introduction

Candida species are among the major pathogenic fungi of humans and commonly colonize the skin, oral cavity, gastrointestinal tract, and genitourinary mucosa[1, 2]. Under normal conditions, *Candida* cells exist as commensal organisms, but when host immunity is compromised, the microbial balance disrupted, or medical interventions such as antibiotics, immunosuppressants, or indwelling catheters are introduced, they can rapidly shift into invasive pathogens that cause mucosal or systemic infections[3]. Among the genus *Candida*, *Candida albicans* has the highest incidence of infection and the greatest host adaptability, accounting for 40-60% of global systemic candidiasis and representing the predominant species in mucosal infections[1, 4, 5]. Meanwhile, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and more recently the multidrug-resistant *Candida auris* have become increasingly important clinical pathogens[6-9]. These species exhibit marked diversity in metabolic adaptation, antifungal tolerance, and immune evasion, suggesting that adaptive evolution under host-imposed pressures is a key determinant of *Candida* pathogenic success[5]. The fungal cell wall, serving as the interface for environmental sensing, signal transduction, and host interaction, is regarded as a critical structural determinant in this adaptive process[10, 11].

Within host tissues, *C. albicans* remodels its cell wall in direct response to local constraints. These programs alter the packing of the β-1,3-glucan/chitin scaffold and the extent of surface β-glucan exposure, thereby tuning Dectin-1 recognition and innate immune activation[12]. For example, lactate, sensed through the cAMP/PKA pathway, favors β-glucan masking in *C. albicans*, whereas acidic pH produces a transient increase in β-glucan visibility that is followed by remasking as pH normalizes and quorum-sensing cues accumulate[13, 14]. This pathogenic fungus adjusts between colonizing and invasive behaviors across different host niches through such context-dependent shifts[15].

With advances in transcriptomics, solid-state NMR, and high resolution electron microscopy, the molecular basis of these cell wall dynamics has been resolved more systematically, including nanoscale models of wall layering and direct compositional readouts in intact material[16]. Notably, cell wall dynamics also occur in other *Candida* species but with species-specific patterns. For instance, *C. auris* that has recently emerged as a global threat to public health frequently exhibits higher chitin content and altered β-1,6-glucan architecture[17, 18]. *C. auris* is recognized as an opportunistic fungal pathogen of significant clinical concern due to its extensive multidrug resistance, which

has been reported to be associated with the enhanced cell wall mechanical stability compared with *C. albicans*[19, 20].

1. The cell wall structure of *C. albicans*

The cell wall of *C. albicans* is a highly organized and multilayered structure that maintains cell shape, protects against osmotic and mechanical stress, and mediates adhesion and immune recognition[10, 21] (Figure 1). Microscopy, biochemistry and molecular genetics consistently identify β-glucans, chitin, and mannoproteins as the principal constituents arranged in a layered, covalently cross-linked network[22, 23].

1.1 β-1,3-glucan

Within this composite, the inner scaffold is built from β-1,3-glucan microfibrils interwoven with chitin, creating the primary load-bearing mesh that determines wall stiffness and elasticity[24]. β-1,3-glucan is synthesized at the plasma membrane by the β-1,3-glucan synthase (catalytic subunit Fks1/Fks2, activated by Rho1). Genetic disruption of *FKS1* establishes this polymer as essential for wall integrity and a major antifungal target of *C. albicans*[25-27].

1.2 Chitin

Chitin is a linear polymer of β-1,4-linked N-acetyl-D-glucosamine that forms tightly hydrogen-bonded microfibrils. It reinforces the inner cell wall by intertwining with β-glucans and forming covalent cross-links via CRH (Congo Red Hypersensitive)-family transglycosylases[28, 29]. *C. albicans* employs multiple chitin synthases, namely Chs1, Chs2, Chs3, and Chs8. Chs1 predominantly governs the formation of the primary septum and integrity. Chs3 supplies the majority of the cell wall chitin. Meanwhile, the activities of Chs2 and Chs8 are crucial for maintaining cell wall integrity under both basal growth conditions and during stress exposure[30-32]. Collectively, this β-glucan/chitin core determines mechanical strength and pore architecture and supplies key PAMPs (notably β-1,3-glucan) in *C. albicans*[19, 33, 34].

1.3 β-1,6-glucan

Covalent continuity between layers is provided by the β-1,6-glucan linker matrix, which connects the inner glucan/chitin scaffold to outer wall proteins and contributes elastic compliance[24, 35]. In *C. albicans*, β-1,6-glucan is a major cell wall polymer, contributing roughly one quarter of total wall mass and ~40% of total β-glucans, and it is organized as a linear β-1,6-linked backbone with sparse β-1,3-glucosyl or laminaribiosyl side

chains that bridge the alkali-insoluble glucan-chitin core to mannoproteins in the outer layer[36]. Its abundance and molecular architecture vary with morphotype, carbon source and stress: hyphal cells and lactate-grown yeast contain less β-1,6-glucan and display shorter, less-branched chains, whereas exposure to short-chain fatty acids or caspofungin increases its apparent molecular weight. Consistent with this plasticity, β-1,6-glucan biosynthesis can compensate when N-/O-mannan elongation or inner-wall chitin/β-1,3-glucan synthesis is impaired, while loss of β-1,6-glucan in KRE6-family backgrounds is associated with severely compromised growth and extensive reorganization of wall architecture[36, 37]. In addition, β-1,6-glucan elicits an immunomodulatory profile distinct from other purified wall polysaccharides, linking this polymer not only to layer-to-layer connectivity but also to how the fungal surface is perceived by host immune receptors[36].

Mechanistically, the biogenesis of β-1,6-glucan is distributed across the secretory pathway and the cell wall, providing a framework for how environmental cues and genetic lesions reshape this linker matrix. Kre5 functions in the ER and is required for efficient β-1,6-glucan production[38]. In the Golgi, Kre6 and Skn1 are required for β-1,6-glucan synthesis and elongation[37, 39]. At the wall, Kre9 and Big1 promote polymer assembly, and marked reductions in cell wall β-1,6-glucan are observed in *kre6 skn1* double mutant, kre9 mutant and big1 mutants[40, 41]. Disrupting these nodes compromises the interface between β-1,6-glucan and GPI-anchored cell wall proteins (CWPs), leading to loss or mis-display of GPI-anchored adhesins such as Als3 and Hwp1, together with broader defects in wall composition, organisation and mechanics[38, 42, 43].

1.4 Mannoprotein

Mannoprotein biogenesis follows a conserved secretory pathway pipeline in *C. albicans*. In the ER, newly synthesized cell wall proteins undergo N-linked glycosylation via the asparagine-linked glycosylation (ALG) pathway, initiate O-linked mannosylation catalyzed by protein O-mannosyltransferases Pmt1, Pmt2, Pmt4, Pmt5, and Pmt6, and acquire a GPI anchor[44, 45]. In the Golgi, α-1,6-mannosyltransferase Och1 initiates the α-1,6-mannan outer chain of N-glycans, while members of the mannan biosynthesis gene 2 (Mnn2) family elaborate α-1,2-mannose branches on N-glycans. Concurrently, the KRE2/MannosylTransferase 1/2 (KRE2/MNT1/2) family extends O-mannans with α-1,2-mannose. Mnn4, together with Mnt3/Mnt5, adds phosphomannan, and β-1,2-mannosyltransferases 1-6 (Bmt1–Bmt6) plus Bmt9 install Candida-specific β-1,2-mannose epitopes on mannans and phospholipomannan

(PLM). The P-type Ca^{2+}/Mn^{2+}-transporting ATPase Pmr1 supplies Mn^{2+} to support Golgi mannosyltransferase activity[46-53]. Glycoside hydrolase family 76 (GH76) proteins Dfg5 and Dcw1 mediate the covalent incorporation and transfer of GPI-anchored cell wall proteins into the β-1,6-glucan network. This step is required for the proper surface display of many GPI-anchored cell wall proteins. Ecm33 further supports accurate GPI-protein presentation and maintains overall cell wall homeostasis[54-57]. The outer cell wall thereby controls hydrophilicity, charge and porosity, modulates nutrient and drug permeability, and dynamically masks or exposes inner β-glucan/chitin to fine-tune interactions with the C-type lectin receptor Dectin-1, the mannose receptor (MR), dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), and Toll-like receptor 2 (TLR2)[21, 33, 58].

Functionally, *C. albicans* wall proteins comprise two cooperating modules: an adhesion (virulence) set and a remodeling set. The former includes ALS adhesins and Hwp1, which establish tissue adhesion spectra, surface colonization, and biofilm maturation[42, 59-61]. In parallel, CFEM (Common in Fungal Extracellular Membrane proteins) family proteins, exemplified by Rbt5, assemble into an extracellular heme-binding relay. This relay enables heme-iron acquisition under host iron limitation, thereby supporting environmental adaptation[62, 63]. The latter centers on GPI-anchored GH72 transglycosylases (Phr1/Phr2) and CRH family of chitin-glucanosyltransferases (Utr2/Crh11/Crh12). Phr1/Phr2 perform cut-and-paste remodeling of β-1,3-glucan with pH-partitioned expression (Phr1 at neutral/alkaline pH, Phr2 in acidic niches), while CRH family forge chitin/β-glucan and chitin/chitin bridges, shaping wall mechanical strength and stress tolerance[64-66].

2. The molecular dialogue between *C. albicans* Pathogen-Associated Molecular Patterns (PAMP) and host Pattern Recognition Receptors (PRR)

The molecules that *C. albicans* presents to the host arise chiefly from its cell wall and nucleic acids. On the host side, CLRs (C-type lectin receptors), TLRs (Toll-like receptors), complement receptors, and the NLRP3 (NOD-like receptor family pyrin domain-containing 3) inflammasome integrate signal cues from the yeast pathogen *C. albicans* to coordinate phagocytosis, killing, and downstream adaptive responses[67-70] (Figure 1). The recognition of β-1,3-glucan from the *C. albicans* cell wall by Dectin-1, a C-type lectin receptor, activates Syk-CARD9 signaling and drives pro-inflammatory programs that are central to antifungal immunity[71]. Human genetic data link the Dectin-1 Y238X variant and CARD9 loss-of-function to heightened susceptibility to

candidiasis, highlighting the importance of this pathway[72-75]. Moreover, multiple C-type lectin receptors are involved in the detection of outer-layer mannans of *C. albicans* to orchestrate distinct immune responses. Dectin-2 and Dectin-3 recognize α-mannan and activate the FcRγ-Syk-CARD9 signaling cascade, promoting IL-23 and IL-1β production with subsequent Th17 responses[76-78]. Meanwhile, the mannose receptor (CD206) and DC-SIGN mediate mannan binding and uptake, thereby modulating dendritic cell polarization and functional outcomes[79-81].

The functions of Toll-like receptors in the recognition of and immune response to *C. albicans* are increasingly being elucidated. Phospholipomannan is recognized by TLR2, and purified *Candida* mannan engages TLR4 to enhance cytokine signaling. In the same innate immune cell, co-engagement of Dectin-1 with TLR2/4 synergistically increases cytokine output[82-85]. Following phagocytosis, fungal DNA and RNA are detected in endosomes by TLR9 and TLR7, respectively, further shaping innate immune programming and promoting antigen presentation. Hyphal growth and related damage signals activate the NLRP3 inflammasome to process IL-1β/IL-18[69, 86-88].

3. Adaptive responses of *C. albicans* cell wall to host environmental signals

To thrive in diverse host niches, *C. albicans* must adapt to varying environmental cues, including differences in carbon sources across body sites, substantial pH fluctuations, and hypoxic environments with elevated CO_2 levels compared to ambient air. Furthermore, during therapeutic interventions, this fungus encounters additional stresses from antifungal drugs. The cell wall of *C. albicans* plays a pivotal role in sensing and responding to these host-derived signals, which is essential for both successful colonization and pathogenesis[89-91]. Host microenvironments modify PAMP surface accessibility, which in turn alters PRR engagement and cytokine output. In the following sections, we will discuss the cell wall response patterns of *C. albicans* in response to key host environmental conditions[13, 92, 93].

3.1 Variable pH conditions in different host compartments

C. albicans must withstand a wide pH spectrum in the host (from the acidic vagina (pH = 4-5) to the near-neutral bloodstream (pH = 7-8)) and dynamically remodels cell wall composition and architecture in response to these fluctuations (Figure 2), thereby influencing how the fungus is detected by innate receptors[13, 91]. pH sensing is mediated primarily by the Rim21-ESCRT (Endosomal Sorting Complex Required for Transport)-Rim101 alkaline response pathway, which partitions wall remodeling genes

with surface glycosidases Phr1 and Phr2: Phr1 is induced at neutral/alkaline pH, whereas Phr2 is preferentially expressed under acidic conditions[94-97]. Under neutral/alkaline conditions, *C. albicans* uses a plasma membrane pH-sensing complex in which the seven-pass protein Rim21, with the auxiliary membrane factors Rim9 and Dfg16, and the β-arrestin-like adaptor Rim8, feeds the signal into the RIM pathway. Upon signal entry, the ESCRT machinery provides the essential platform for activation. The Bro1-domain scaffold Rim20 associates with ESCRT-III (e.g., Snf7) and positions the calpain-like protease Rim13 to cleave the C-terminus of Rim101, generating the transcriptionally active N-terminal fragment that enters the nucleus[98-101]. Once in the nucleus, Rim101 launches the neutral/alkaline program, upregulating *PHR1* while repressing the acidic program gene *PHR2*. The GPI-linked chitinase Cht2 is also elevated at neutral/alkaline pH under Rim101 control, with Bcr1 contributing in specific surface-display contexts. As a consequence, β-1,3-glucan remodeling is reinforced and inner-layer accessibility is reduced compared with acidic growth[13, 65, 97, 102-105].

Under acidic conditions, Rim101 processing is curtailed in *C. albicans*. Accordingly, *PHR1* and *CHT2* decline while *PHR2* persists, and the surface shows increased exposure of β-1,3-glucan together with increased chitin exposure, which correlates with enhanced myeloid recognition and cytokine output[13]. Crucially, the pH-driven wall architecture and visibility are rapid and reversible: β-glucan exposed at low pH can be re-masked within hours after a return to neutral pH, a process modulated in part by quorum-sensing molecules (e.g., farnesol) and by the capacity of the wall-assembly machinery[104]. Moreover, *C. albicans* ESCRT mutants, which cannot properly activate Rim101, fail to process Rim101 and display attenuated virulence in murine infection models, indicating that the pH-sensing/ESCRT arm contributes to pathogenic fitness under host pressures[98].

In alkaline adaptation, *C. albicans* utilizes the calcineurin/Crz1 pathway in parallel with Rim101, supporting cell wall homeostasis and pH-responsive transcription[106, 107]. At the protein level, neutral/alkaline growth upregulates key wall adhesins and effector factors, including Als3, Hwp1, Hyr1, Rbt1/Rbt4, and host-interaction proteins Pra1 (zincophore) and Ece1 (the candidalysin precursor), consistent with pH-driven remodeling of the displayed wall proteome[15, 108, 109]. The cell wall integrity pathway (Pkc1-Bck1-Mkk2-Mkc1) functions as an execution-layer buffer for pH-triggered secondary wall stress, tuning mechanics while acting as a collaborator rather than a primary pH sensor[110-112]. In host niches, these pH-tuned shifts in *C. albicans* modulate β-glucan accessibility to innate PRRs, recalibrate adhesion and epithelial-damage potential, and enable micronutrient scavenging, thereby shaping recognition and

virulence outcomes *in vivo*[13].

3.2 Hypoxia and elevated CO_2 levels in host niches

Across human niches, *C. albicans* encounters distinct O_2/CO_2 levels: ~1-2% O_2 at the colonic epithelium (physiologic hypoxia), ~0.5-1% O_2 in the resting vaginal lumen, ~1.7-5.5% O_2 within the uterine cavity, and alveolar gas contains ~5% CO_2[113, 114]. In these environments, hypoxia engages mitochondria-dependent cAMP/PKA signaling pathway that rapidly reduces the surface accessibility of inner β-1,3-glucan, thereby lowering Dectin-1 recognition and inflammatory output[92, 115]. This hypoxia-induced masking of *C. albicans* has been shown both *in vitro* and in infection models. Within the PKA module, the catalytic subunits Tpk1 and Tpk2 act downstream of Cyr1 to execute wall-relevant outputs: Tpk1 is biased toward cell wall integrity and surface protein control, whereas Tpk2 is a major regulator of dimorphism and adhesion. Both Tpk1 and Tpk2 contribute, with partial redundancy, to environmental control of β-glucan exposure[116, 117]. At the interface level, hypoxia consistently decreases β-1,3-glucan accessibility and yields a surface that appears more mannoprotein-dominated in presentation, further concealing the underlying chitin/β-glucan scaffold from PRRs[92, 118].

On the CO_2 side, carbonic anhydrase Nce103 provides bicarbonate that directly activates Cyr1, boosting PKA and upregulating wall/effector genes, such as *ALS3*, *HWP1*, and *ECE1*. Importantly, CO_2 itself does not trigger masking, but the Sch9-Rca1-Nce103 module tunes the baseline of β-1,3-glucan exposure across hypoxia and lactate contexts[119-124]. In parallel, the intrinsically disordered region of PP2C phosphatase Ptc2 acts as the direct CO_2 sensor via phase separation in *C. albicans*, providing a carbonic anhydrase-independent input into morphogenesis and wall assembly control[125].

Low O_2 together with elevated CO_2 stabilizes the oxygen-responsive regulator Ume6 via the Ofd1-Ume6 axis, sustaining hyphal growth and increasing display of wall/effector proteins including Als3, Hwp1, and Ece1[126-128]. Under hypoxia, Upc2- and Bcr1-dependent induction of CFEM family genes, such as *RBT5* and *PGA7*, establishes an extracellular heme-uptake relay across the wall that supports growth under nutritional immunity[129-131].

3.3 Variable carbon nutrient availability

In host niches, readily utilizable carbon is often biased toward organic acids and non-glucose substrates. Lactate and acetate are abundant in the gut/vagina, and amino

acids, fatty acids, or GlcNAc (N-acetylglucosamine) predominate within phagosomes or inflamed tissues (Figure 3). Therefore, *C. albicans* reads these cues to remodel cell wall composition and layering, maintaining wall integrity under low glucose conditions while tuning β-glucan exposure[14, 90, 93, 132-135].

When grown on lactate rather than glucose, *C. albicans* reduces surface β-1,3-glucan exposure via a Gpr1-dependent, Crz1-mediated pathway, effectively presenting a mannoprotein-biased interface over the inner PAMP-rich scaffold. The cell wall is overall thinner with altered nanomechanics in lactate, consistent with reduced Dectin-1 accessibility despite similar bulk polysaccharide classes[10, 14, 90, 136].

With acetate and other non-fermentable carbon sources, derepression via the SNF1/AMPK-Mig1/2 system couples to the cell wall integrity MAPK branch (Pkc1-Bck1-Mkk2-Mkc1/Rlm1), reprogramming β-glucan/chitin synthetic and cross-linking genes while maintaining the mannoprotein/β-1,6-glucan linkage network. Genetically, the transcription factor Rlm1 controls carbon adaptation outputs at the wall and impacts fungal-immune interactions[137-139].

GlcNAc functions as both nutrient and signal in *C. albicans*: Ngt1-dependent uptake and Ngs1-dependent transcription activate hyphal programs and upregulate wall/effector genes, increasing the functional repertoire of the mannoprotein coat. Furthermore, GlcNAc signaling is capable of tuning pore architecture and surface charge without necessarily increasing total β-glucan, thereby limiting Dectin-1 access through remodeling of the outer interface[140-142].

C. albicans demonstrates a markedly higher efficiency in utilizing amino acids as a carbon source compared to other fungal species, and these amino acids serve as a crucial nutrient supply following phagocytosis. When amino acids are abundant, the SPS (Ssy1/Ptr3/Ssy5)-Stp2 pathway promotes uptake and catabolism, mitochondrial proline oxidation via Put1/Put2 activates cAMP-PKA to elevate hyphal and wall programs. Furthermore, amino acid catabolism releases ammonia that alkalinizes acidic niches (e.g., phagosomes), biasing assembly toward a Rim101/PHR1-type neutral/alkaline wall with reduced β-glucan accessibility and improved leukocyte escape[135, 143, 144].

Taken together, distinct carbon inputs converge on two coordinated wall outputs: (i) resetting the accessibility, density, and cross-linking of inner β-glucan/chitin, and (ii) reallocating and functionalizing the outer mannoprotein/GPI-CWP coat. Consequently, this carbon-programmed plasticity lowers innate-receptor access (e.g., Dectin-1) while sustaining adhesion, biofilm maturation, and stress tolerance in low-glucose, organic-

acid-rich, immune-pressured niches[14, 90, 93, 115, 133, 145].

3.4 Antifungal drugs

Upon exposure to antifungal drugs, *C. albicans* deploys rapid, plastic, cell wall-centered programs that sustain survival, recalibrate immune visibility, and promote tolerance or resistance[11, 17]. Antifungal drugs typically belong to one of three main classes: echinocandins, azoles, and polyenes. Echinocandins, the first-line drugs for the treatment of systemic candidiasis, inhibit β-1,3-glucan synthase Fks1, and resistance often maps to *FKS1* hotspot mutations that lower drug-target affinity. Inhibition of glucan synthesis immediately activates the cell wall damage response together with Ca^{2+}-calcineurin (Crz1) and HOG branches, elevating chitin synthesis and cross-linking to compensate for loss of β-glucan[146-148]. The transcription factor Cas5 is a central regulator of the echinocandin-induced wall damage response, driving expression of wall remodeling and secretion/ER genes. The *cas5* mutant strain is hypersensitive to echinocandins. Cas5 acts alongside transcription factors Sko1 and Rlm1 in an expanded wall stress network (with Ada2 as a co-activator in specific contexts)[149-151]. The Hsp90-calcineurin axis is also pivotal for echinocandin tolerance, and its inhibition can convert echinocandins from fungistatic to fungicidal in certain settings[152]. During growth in echinocandins, cells frequently show β-1,3-glucan unmasking, increasing Dectin-1 accessibility and modulating inflammatory outputs. Although azoles primarily target ergosterol biosynthesis, they secondarily induce wall stress and trigger wall-remodeling programs. The wall-associated factors, such as Ecm33, contribute to outer-layer regeneration and surface display during stress and recovery in response to azoles[57, 153-156].

Moreover, *C. albicans* can form biofilms, wherein the extracellular matrix acts as a diffusion and sequestration barrier that limits the drug access, thereby contributing to therapeutic resistance. The β-1,3-glucan in matrix binds antifungals and contributes substantially to multidrug tolerance[157, 158]. Delivery of glucan from the wall to the matrix depends on β-1,3-glucosyltransferase Bgl2, glycosidase Phr1, and β-1,3-glucanase Xog1, establishing a dedicated pathway for matrix glucan accumulation. In addition, the transcription factor Csr1 negatively regulates soluble matrix β-1,3-glucan to tune overall matrix output and drug tolerance[159, 160].

3.5 Iron restriction and metal availability

Host nutritional immunity restricts access to transition metals such as iron, copper, zinc, and manganese, and experimentally altering the availability of these metals remodels *C. albicans* cell wall architecture and β-1,3-glucan exposure in a metal-specific

manner[161, 162]. Under iron-poor conditions relevant to host niches, *C. albicans* increases total cell wall biomass and thickens both the inner glucan–chitin scaffold and the outer mannan layer while strongly reducing surface β-1,3-glucan exposure, yielding a pronounced masked phenotype that attenuates innate immune activation[34, 162]. This iron-limitation program depends on the high-affinity iron permease Ftr1, the iron-responsive transcription factor Sef1 and protein kinase A, and is accompanied by broad changes in the expression of genes involved in cell wall synthesis, remodelling and glycosylation that collectively reinforce a mannan-rich shield over the glucan core[115, 162]. In contrast, iron-replete conditions are associated with reduced mannan and chitin content, increased β-1,3-glucan mass and exposure, and enhanced recognition and killing by phagocytes, indicating that reciprocal changes in iron availability drive opposing configurations of wall composition and PAMP display. Changes in iron levels also modulate intracellular lactate, Ca^{2+}-calcineurin (Crz1) activity and Cek1 MAPK phosphorylation, linking central carbon metabolism to alterations in wall composition, stress responses and susceptibility to cell-wall-active antifungals[163]. Iron-regulated factors such as the α-1,2-mannosyltransferase Mnn5, the ferric reductase Cfl1 and the Mrs4-Ccc1-Smf3 iron-trafficking pathway further couple iron homeostasis to N-/O-mannan elaboration, cell wall integrity signalling, morphogenesis and virulence, underscoring that iron availability is closely integrated with the genetic circuitry that shapes cell wall structure in *C. albicans*[164-166].

Other transition metals have also been shown to induce distinct, metal-specific programs of cell wall remodelling and PAMP exposure. Zinc limitation triggers a characteristic “Goliath” phenotype in *C. albicans*, in which cells become enlarged, hyper-adherent and display increased chitin exposure at the surface; this response is controlled by the zinc-responsive regulator Zap1 and reflects a Zn-dependent reconfiguration of wall composition and adhesin expression[167, 168]. In contrast to iron and copper limitation, which reduce β-1,3-glucan exposure and promote masking, zinc or manganese limitation increases β-1,3-glucan exposure, indicating that different metal stresses drive the wall towards either masking or unmasking states[162, 169]. Perturbation of manganese homeostasis leads to marked unmasking of β-1,3-glucan and chitin, heightened sensitivity to cell wall stress and enhanced Dectin-1-dependent recognition, through mechanisms that involve changes in glucanase activity rather than calcineurin signalling. Together, these observations show that manipulating zinc or manganese availability, alongside iron, reproducibly engages metal-specific remodelling programs that alter cell wall thickness, polysaccharide composition and PAMP display in *C. albicans*[115, 167, 169].

4. Differences in cell wall architectures between *C. albicans* and *C. auris*

Both *C. albicans* and *C. auris* possess an inner β-1,3-glucan/chitin scaffold overlaid by an outer mannoprotein layer. However, *C. auris* generally presents a more dominant outer mannan coat with lower baseline surface β-glucan accessibility, reducing Dectin-1 recognition and dampening innate activation[170, 171]. In addition, *C. auris* lacks clear orthologs of Ece1 (a key cytolytic peptide toxin) and Hwp1 (an important adhesin on the cell surface) found in *C. albicans*, suggesting a greater reliance on mannan-based shielding and alternative adhesin/wall-protein repertoires[172, 173].

C. albicans responds strongly to host-relevant carbon sources. For example, lactate induces β-glucan masking. The surface exposure of β-glucan is further trimmed by β-1,3-glucanases Xog1 and Eng1, thereby lowering Dectin-1 engagement and reshaping the PAMP landscape in the cell wall[14, 174, 175]. By contrast, *C. auris* displays lower baseline β-glucan exposure and shows strain- and condition-dependent but often limited unmasking in response to carbon or drug perturbations[170, 171]. Upon β-1,3-glucan inhibition by echinocandins, both species exhibit wall-state changes at the polysaccharide level: caspofungin rigidifies β-1,6-glucans and mannan sidechains and reduces water permeability during β-1,3-glucan depletion. Downstream remodeling, however, diverges between species: *C. albicans* commonly shows wall thickening together with altered chitin and β-glucan dynamics, whereas *C. auris* tends to preserve wall integrity via β-1,6-glucan upregulation rather than prominent thickening. Consistent with a heightened dependence on β-1,6-glucan-mediated adaptation, genetic disruption of β-1,6-glucan synthase in *C. auris* alters echinocandin susceptibility, further highlighting β-1,6-glucan as a critical node in *C. auris* cell-wall remodeling under echinocandin pressure. Together, these features align with a strategy in which *C. auris* more often maintains a low-visibility interface through a dominant mannan coat and glycosylation-linked remodeling, with unmasking being limited even under β-1,3-glucan-targeting stress[20, 115, 176, 177].

Conclusions

The fungal cell wall is a dynamic organelle that marries elasticity and selective permeability with tensile strength and spatial order, preserving cell morphology while buffering osmotic and mechanical stress. *C. albicans* cell wall shows a layered design with an inner β-1,3-glucan/chitin framework coupled to an outer mannoprotein/GPI-

CWP coat. It functions both as armour and as an interface, filtering drugs and peptides, coordinating nutrient exchange, and presenting ligands to host pattern-recognition receptors. The wall synthesis, cross-linking, and surface display are continually recalibrated to pH, O_2/CO_2, carbon source, metal availability, and immune effectors through integrated signaling circuits (e.g., Rim101, cAMP/PKA, SNF1/AMPK, calcineurin, HOG pathway). This plasticity underpins tolerance to antifungal drugs and compensates for deleterious mutations. It should be noted that polymers in *C. albicans* cell wall also carry immunostimulatory PAMPs that trigger antifungal defense when exposed. As a pathogenic yeast, *C. albicans* exploit this trade-off by modulating PAMP accessibility and reshaping the outer protein repertoire. Additionally, biofilm matrix extends communication and collective protection. In clinical niches, *C. albicans* integrates host-derived cues, such as lactate, iron restriction, and hypoxia, to induce β-glucan masking, adjust mannoprotein display, and stabilize biofilms, thereby reducing innate recognition while maintaining growth. Viewing the wall as a programmable interface explains how it simultaneously mediates virulence yet remains an exploitable therapeutic vulnerability, pointing to interventions that force PAMP exposure while blocking compensatory rebuilding.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (32470075 to Y.L., 82373493 to C.S.).

Reference

[1] Lass-Flörl C, Kanj S S, Govender N P, et al. Invasive candidiasis [J]. *Nature Reviews Disease Primers*, 2024, 10(1).

[2] Pfaller M A, Diekema D J. Epidemiology of invasive candidiasis: a persistent public health problem [J]. *Clin Microbiol Rev*, 2007, 20(1): 133-63.

[3] Bassetti M, Vena A, Giacobbe D R, et al. Risk Factors for Intra-Abdominal Candidiasis in Intensive Care Units: Results from EUCANDICU Study [J]. *Infect Dis Ther*, 2022, 11(2): 827-40.

[4] Morschhäuser J. Adaptation of Candida albicans to specific host environments by gain-of-function mutations in transcription factors [J]. *PLoS Pathog*, 2024, 20(11): e1012643.

[5] Mayer F L, Wilson D, Hube B. Candida albicans pathogenicity mechanisms [J]. *Virulence*, 2013, 4(2): 119-28.

[6] Bhargava A, Klamer K, Sharma M, et al. Candida auris: A Continuing Threat [J]. *Microorganisms*, 2025, 13(3).

[7] Pfaller M A, Diekema D J, Turnidge J D, et al. Twenty Years of the SENTRY Antifungal

Surveillance Program: Results for Candida Species From 1997-2016 [J]. *Open Forum Infect Dis*, 2019, 6(Suppl 1): S79-s94.

[8] Silva S, Negri M, Henriques M, et al. Candida glabrata, Candida parapsilosis and Candida tropicalis: biology, epidemiology, pathogenicity and antifungal resistance [J]. *FEMS Microbiol Rev*, 2012, 36(2): 288-305.

[9] Eix E F, Nett J E. Candida auris: Epidemiology and Antifungal Strategy [J]. *Annu Rev Med*, 2025, 76(1): 57-67.

[10] Gow N a R, Latge J P, Munro C A. The Fungal Cell Wall: Structure, Biosynthesis, and Function [J]. *Microbiol Spectr*, 2017, 5(3).

[11] Hopke A, Brown A J P, Hall R A, et al. Dynamic Fungal Cell Wall Architecture in Stress Adaptation and Immune Evasion [J]. *Trends Microbiol*, 2018, 26(4): 284-95.

[12] Gow N a R, Hube B. Importance of the Candida albicans cell wall during commensalism and infection [J]. *Current Opinion in Microbiology*, 2012, 15(4): 406-12.

[13] Sherrington S L, Sorsby E, Mahtey N, et al. Adaptation of Candida albicans to environmental pH induces cell wall remodelling and enhances innate immune recognition [J]. *PLoS Pathog*, 2017, 13(5): e1006403.

[14] Ballou E R, Avelar G M, Childers D S, et al. Lactate signalling regulates fungal β-glucan masking and immune evasion [J]. *Nat Microbiol*, 2016, 2: 16238.

[15] Childers D S, Avelar G M, Bain J M, et al. Impact of the Environment upon the Candida albicans Cell Wall and Resultant Effects upon Immune Surveillance [J]. *Curr Top Microbiol Immunol*, 2020, 425: 297-330.

[16] Gow N a R. Fungal cell wall biogenesis: structural complexity, regulation and inhibition [J]. *Fungal Genet Biol*, 2025, 179: 103991.

[17] Banda-Flores I A, Torres-Tirado D, Mora-Montes H M, et al. Resilience in Resistance: The Role of Cell Wall Integrity in Multidrug-Resistant Candida [J]. *J Fungi (Basel)*, 2025, 11(4).

[18] Fernando L D, Dickwella Widanage M C, Shekar S C, et al. Solid-state NMR analysis of unlabeled fungal cell walls from Aspergillus and Candida species [J]. *J Struct Biol X*, 2022, 6: 100070.

[19] Lenardon M D, Sood P, Dorfmueller H C, et al. Scalar nanostructure of the Candida albicans cell wall; a molecular, cellular and ultrastructural analysis and interpretation [J]. *Cell Surf*, 2020, 6: 100047.

[20] Dickwella Widanage M C, Singh K, Li J, et al. Distinct echinocandin responses of Candida albicans and Candida auris cell walls revealed by solid-state NMR [J]. *Nat Commun*, 2025, 16(1): 6295.

[21] Hall R A, Gow N A. Mannosylation in Candida albicans: role in cell wall function and immune recognition [J]. *Mol Microbiol*, 2013, 90(6): 1147-61.

[22] Bowman S M, Free S J. The structure and synthesis of the fungal cell wall [J]. *Bioessays*, 2006, 28(8): 799-808.

[23] Klis F M, De Groot P, Hellingwerf K. Molecular organization of the cell wall of Candida albicans [J]. *Med Mycol*, 2001, 39 Suppl 1: 1-8.

[24] Ruiz-Herrera J, Elorza M V, Valentín E, et al. Molecular organization of the cell wall of Candida albicans and its relation to pathogenicity [J]. *FEMS Yeast Res*, 2006, 6(1): 14-29.

[25] Douglas C M, D'ippolito J A, Shei G J, et al. Identification of the FKS1 gene of Candida albicans as the essential target of 1,3-beta-D-glucan synthase inhibitors [J]. *Antimicrob*

Agents Chemother, 1997, 41(11): 2471-9.

[26] Lesage G, Bussey H. Cell wall assembly in Saccharomyces cerevisiae [J]. *Microbiol Mol Biol Rev*, 2006, 70(2): 317-43.

[27] Mio T, Adachi-Shimizu M, Tachibana Y, et al. Cloning of the Candida albicans homolog of Saccharomyces cerevisiae GSC1/FKS1 and its involvement in beta-1,3-glucan synthesis [J]. *J Bacteriol*, 1997, 179(13): 4096-105.

[28] Lenardon M D, Munro C A, Gow N A. Chitin synthesis and fungal pathogenesis [J]. *Curr Opin Microbiol*, 2010, 13(4): 416-23.

[29] Arroyo J, Farkaš V, Sanz A B, et al. 'Strengthening the fungal cell wall through chitin-glucan cross-links: effects on morphogenesis and cell integrity' [J]. *Cell Microbiol*, 2016, 18(9): 1239-50.

[30] Munro C A, Winter K, Buchan A, et al. Chs1 of Candida albicans is an essential chitin synthase required for synthesis of the septum and for cell integrity [J]. *Mol Microbiol*, 2001, 39(5): 1414-26.

[31] Lenardon M D, Whitton R K, Munro C A, et al. Individual chitin synthase enzymes synthesize microfibrils of differing structure at specific locations in the Candida albicans cell wall [J]. *Mol Microbiol*, 2007, 66(5): 1164-73.

[32] Preechasuth K, Anderson J C, Peck S C, et al. Cell wall protection by the Candida albicans class I chitin synthases [J]. *Fungal Genet Biol*, 2015, 82: 264-76.

[33] Garcia-Rubio R, De Oliveira H C, Rivera J, et al. The Fungal Cell Wall: Candida, Cryptococcus, and Aspergillus Species [J]. *Front Microbiol*, 2019, 10: 2993.

[34] Hameed S, Hans S, Singh S, et al. Revisiting the Vital Drivers and Mechanisms of β-Glucan Masking in Human Fungal Pathogen, Candida albicans [J]. *Pathogens*, 2021, 10(8).

[35] Kollár R, Reinhold B B, Petráková E, et al. Architecture of the yeast cell wall. Beta(1-->6)-glucan interconnects mannoprotein, beta(1-->)3-glucan, and chitin [J]. *J Biol Chem*, 1997, 272(28): 17762-75.

[36] Bekirian C, Valsecchi I, Bachellier-Bassi S, et al. β-1,6-Glucan plays a central role in the structure and remodeling of the bilaminate fungal cell wall [J]. *Elife*, 2024, 13.

[37] Han Q, Wang N, Yao G, et al. Blocking β-1,6-glucan synthesis by deleting KRE6 and SKN1 attenuates the virulence of Candida albicans [J]. *Mol Microbiol*, 2019, 111(3): 604-20.

[38] Herrero A B, Magnelli P, Mansour M K, et al. KRE5 gene null mutant strains of Candida albicans are avirulent and have altered cell wall composition and hypha formation properties [J]. *Eukaryot Cell*, 2004, 3(6): 1423-32.

[39] Mio T, Yamada-Okabe T, Yabe T, et al. Isolation of the Candida albicans homologs of Saccharomyces cerevisiae KRE6 and SKN1: expression and physiological function [J]. *J Bacteriol*, 1997, 179(7): 2363-72.

[40] Umeyama T, Kaneko A, Watanabe H, et al. Deletion of the CaBIG1 gene reduces beta-1,6-glucan synthesis, filamentation, adhesion, and virulence in Candida albicans [J]. *Infect Immun*, 2006, 74(4): 2373-81.

[41] Lussier M, Sdicu A M, Shahinian S, et al. The Candida albicans KRE9 gene is required for cell wall beta-1, 6-glucan synthesis and is essential for growth on glucose [J]. *Proc Natl Acad Sci U S A*, 1998, 95(17): 9825-30.

[42] Staab J F, Bradway S D, Fidel P L, et al. Adhesive and mammalian transglutaminase substrate properties of Candida albicans Hwp1 [J]. *Science*, 1999, 283(5407): 1535-8.

[43] Hoyer L L, Oh S H, Jones R, et al. A proposed mechanism for the interaction between the Candida albicans Als3 adhesin and streptococcal cell wall proteins [J]. *Front Microbiol*, 2014, 5: 564.

[44] Prill S K, Klinkert B, Timpel C, et al. PMT family of Candida albicans: five protein mannosyltransferase isoforms affect growth, morphogenesis and antifungal resistance [J]. *Mol Microbiol*, 2005, 55(2): 546-60.

[45] Larkin A, Imperiali B. The expanding horizons of asparagine-linked glycosylation [J]. *Biochemistry*, 2011, 50(21): 4411-26.

[46] Hernández-Chávez M J, Clavijo-Giraldo D M, Novák Á, et al. Role of Protein Mannosylation in the Candida tropicalis-Host Interaction [J]. *Front Microbiol*, 2019, 10: 2743.

[47] Hall R A, Bates S, Lenardon M D, et al. The Mnn2 mannosyltransferase family modulates mannoprotein fibril length, immune recognition and virulence of Candida albicans [J]. *PLoS Pathog*, 2013, 9(4): e1003276.

[48] Munro C A, Bates S, Buurman E T, et al. Mnt1p and Mnt2p of Candida albicans are partially redundant alpha-1,2-mannosyltransferases that participate in O-linked mannosylation and are required for adhesion and virulence [J]. *J Biol Chem*, 2005, 280(2): 1051-60.

[49] Díaz-Jiménez D F, Mora-Montes H M, Hernández-Cervantes A, et al. Biochemical characterization of recombinant Candida albicans mannosyltransferases Mnt1, Mnt2 and Mnt5 reveals new functions in O- and N-mannan biosynthesis [J]. *Biochem Biophys Res Commun*, 2012, 419(1): 77-82.

[50] González-Hernández R J, Jin K, Hernández-Chávez M J, et al. Phosphomannosylation and the Functional Analysis of the Extended Candida albicans MNN4-Like Gene Family [J]. *Front Microbiol*, 2017, 8: 2156.

[51] Courjol F, Jouault T, Mille C, et al. β-1,2-Mannosyltransferases 1 and 3 Participate in Yeast and Hyphae O- and N-Linked Mannosylation and Alter Candida albicans Fitness During Infection [J]. *Open Forum Infect Dis*, 2015, 2(3): ofv116.

[52] Mille C, Bobrowicz P, Trinel P A, et al. Identification of a new family of genes involved in beta-1,2-mannosylation of glycans in Pichia pastoris and Candida albicans [J]. *J Biol Chem*, 2008, 283(15): 9724-36.

[53] Sfihi-Loualia G, Hurtaux T, Fabre E, et al. Candida albicans β-1,2-mannosyltransferase Bmt3 prompts the elongation of the cell-wall phosphopeptidomannan [J]. *Glycobiology*, 2016, 26(2): 203-14.

[54] Ao J, Chinnici J L, Maddi A, et al. The N-Linked Outer Chain Mannans and the Dfg5p and Dcw1p Endo-α-1,6-Mannanases Are Needed for Incorporation of Candida albicans Glycoproteins into the Cell Wall [J]. *Eukaryot Cell*, 2015, 14(8): 792-803.

[55] Razmi M, Kim J, Chinnici J, et al. Candida albicans Mannosidases, Dfg5 and Dcw1, Are Required for Cell Wall Integrity and Pathogenesis [J]. *J Fungi (Basel)*, 2024, 10(8).

[56] Martinez-Lopez R, Park H, Myers C L, et al. Candida albicans Ecm33p is important for normal cell wall architecture and interactions with host cells [J]. *Eukaryot Cell*, 2006, 5(1): 140-7.

[57] Gil-Bona A, Reales-Calderon J A, Parra-Giraldo C M, et al. The Cell Wall Protein Ecm33 of Candida albicans is Involved in Chronological Life Span, Morphogenesis, Cell Wall Regeneration, Stress Tolerance, and Host-Cell Interaction [J]. *Front Microbiol*, 2016, 7: 64.

[58] Masuoka J, Hazen K C. Cell wall mannan and cell surface hydrophobicity in Candida albicans serotype A and B strains [J]. *Infect Immun*, 2004, 72(11): 6230-6.

[59] Hoyer L L, Green C B, Oh S H, et al. Discovering the secrets of the Candida albicans agglutinin-like sequence (ALS) gene family--a sticky pursuit [J]. *Med Mycol*, 2008, 46(1): 1-15.

[60] Nobile C J, Schneider H A, Nett J E, et al. Complementary adhesin function in C. albicans biofilm formation [J]. *Curr Biol*, 2008, 18(14): 1017-24.

[61] Kumari A, Tripathi A H, Gautam P, et al. Adhesins in the virulence of opportunistic fungal pathogens of human [J]. *Mycology*, 2021, 12(4): 296-324.

[62] Kuznets G, Vigonsky E, Weissman Z, et al. A relay network of extracellular heme-binding proteins drives C. albicans iron acquisition from hemoglobin [J]. *PLoS Pathog*, 2014, 10(10): e1004407.

[63] Roy U, Yaish S, Weissman Z, et al. Ferric reductase-related proteins mediate fungal heme acquisition [J]. *Elife*, 2022, 11.

[64] Kováčová K, Degani G, Stratilová E, et al. Catalytic properties of Phr family members of cell wall glucan remodeling enzymes: implications for the adaptation of Candida albicans to ambient pH [J]. *FEMS Yeast Res*, 2015, 15(2).

[65] Popolo L, Degani G, Camilloni C, et al. The PHR Family: The Role of Extracellular Transglycosylases in Shaping Candida albicans Cells [J]. *J Fungi (Basel)*, 2017, 3(4).

[66] Fang W, Sanz A B, Bartual S G, et al. Mechanisms of redundancy and specificity of the Aspergillus fumigatus Crh transglycosylases [J]. *Nat Commun*, 2019, 10(1): 1669.

[67] Bourgeois C, Majer O, Frohner I E, et al. Fungal attacks on mammalian hosts: pathogen elimination requires sensing and tasting [J]. *Curr Opin Microbiol*, 2010, 13(4): 401-8.

[68] Netea M G, Brown G D, Kullberg B J, et al. An integrated model of the recognition of Candida albicans by the innate immune system [J]. *Nat Rev Microbiol*, 2008, 6(1): 67-78.

[69] Hise A G, Tomalka J, Ganesan S, et al. An essential role for the NLRP3 inflammasome in host defense against the human fungal pathogen Candida albicans [J]. *Cell Host Microbe*, 2009, 5(5): 487-97.

[70] Hardison S E, Brown G D. C-type lectin receptors orchestrate antifungal immunity [J]. *Nat Immunol*, 2012, 13(9): 817-22.

[71] Marakalala M J, Vautier S, Potrykus J, et al. Differential adaptation of Candida albicans in vivo modulates immune recognition by dectin-1 [J]. *PLoS Pathog*, 2013, 9(4): e1003315.

[72] Ferwerda B, Ferwerda G, Plantinga T S, et al. Human dectin-1 deficiency and mucocutaneous fungal infections [J]. *N Engl J Med*, 2009, 361(18): 1760-7.

[73] Tang J, Lin G, Langdon W Y, et al. Regulation of C-Type Lectin Receptor-Mediated Antifungal Immunity [J]. *Front Immunol*, 2018, 9: 123.

[74] Tang C, Liu Y, Long J, et al. Clinical features of patients with fungal infections caused by CARD9 deficiency: a literature review of case reports [J]. *Front Cell Infect Microbiol*, 2025, 15: 1615929.

[75] Glocker E O, Hennigs A, Nabavi M, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections [J]. *N Engl J Med*, 2009, 361(18): 1727-35.

[76] Sato K, Yang X L, Yudate T, et al. Dectin-2 is a pattern recognition receptor for fungi that couples with the Fc receptor gamma chain to induce innate immune responses [J]. *J Biol Chem*, 2006, 281(50): 38854-66.

[77] Saijo S, Ikeda S, Yamabe K, et al. Dectin-2 recognition of alpha-mannans and induction of Th17 cell differentiation is essential for host defense against Candida albicans [J]. *Immunity*, 2010, 32(5): 681-91.

[78] Zhu L L, Zhao X Q, Jiang C, et al. C-type lectin receptors Dectin-3 and Dectin-2 form a heterodimeric pattern-recognition receptor for host defense against fungal infection [J]. *Immunity*, 2013, 39(2): 324-34.

[79] Cambi A, Netea M G, Mora-Montes H M, et al. Dendritic cell interaction with Candida albicans critically depends on N-linked mannan [J]. *J Biol Chem*, 2008, 283(29): 20590-9.

[80] Van De Veerdonk F L, Marijnissen R J, Kullberg B J, et al. The macrophage mannose receptor induces IL-17 in response to Candida albicans [J]. *Cell Host Microbe*, 2009, 5(4): 329-40.

[81] Pellon A, Sadeghi Nasab S D, Moyes D L. New Insights in Candida albicans Innate Immunity at the Mucosa: Toxins, Epithelium, Metabolism, and Beyond [J]. *Front Cell Infect Microbiol*, 2020, 10: 81.

[82] Netea M G, Gow N A, Munro C A, et al. Immune sensing of Candida albicans requires cooperative recognition of mannans and glucans by lectin and Toll-like receptors [J]. *J Clin Invest*, 2006, 116(6): 1642-50.

[83] Jouault T, Ibata-Ombetta S, Takeuchi O, et al. Candida albicans phospholipomannan is sensed through toll-like receptors [J]. *J Infect Dis*, 2003, 188(1): 165-72.

[84] Roeder A, Kirschning C J, Rupec R A, et al. Toll-like receptors and innate antifungal responses [J]. *Trends Microbiol*, 2004, 12(1): 44-9.

[85] Ferwerda G, Meyer-Wentrup F, Kullberg B J, et al. Dectin-1 synergizes with TLR2 and TLR4 for cytokine production in human primary monocytes and macrophages [J]. *Cell Microbiol*, 2008, 10(10): 2058-66.

[86] Gow N A, Van De Veerdonk F L, Brown A J, et al. Candida albicans morphogenesis and host defence: discriminating invasion from colonization [J]. *Nat Rev Microbiol*, 2011, 10(2): 112-22.

[87] Biondo C, Malara A, Costa A, et al. Recognition of fungal RNA by TLR7 has a nonredundant role in host defense against experimental candidiasis [J]. *Eur J Immunol*, 2012, 42(10): 2632-43.

[88] Patin E C, Thompson A, Orr S J. Pattern recognition receptors in fungal immunity [J]. *Semin Cell Dev Biol*, 2019, 89: 24-33.

[89] Shao T Y, Haslam D B, Bennett R J, et al. Friendly fungi: symbiosis with commensal Candida albicans [J]. *Trends Immunol*, 2022, 43(9): 706-17.

[90] Alves R, Barata-Antunes C, Casal M, et al. Adapting to survive: How Candida overcomes host-imposed constraints during human colonization [J]. *PLoS Pathog*, 2020, 16(5): e1008478.

[91] Hall R A. Dressed to impress: impact of environmental adaptation on the Candida albicans cell wall [J]. *Mol Microbiol*, 2015, 97(1): 7-17.

[92] Pradhan A, Avelar G M, Bain J M, et al. Hypoxia Promotes Immune Evasion by Triggering β-Glucan Masking on the Candida albicans Cell Surface via Mitochondrial and cAMP-Protein Kinase A Signaling [J]. *mBio*, 2018, 9(6).

[93] Ene I V, Adya A K, Wehmeier S, et al. Host carbon sources modulate cell wall architecture, drug resistance and virulence in a fungal pathogen [J]. *Cell Microbiol*, 2012, 14(9): 1319-

35.
[94] Davis D, Edwards J E, Jr., Mitchell A P, et al. Candida albicans RIM101 pH response pathway is required for host-pathogen interactions [J]. *Infect Immun*, 2000, 68(10): 5953-9.
[95] Mühlschlegel F A, Fonzi W A. PHR2 of Candida albicans encodes a functional homolog of the pH-regulated gene PHR1 with an inverted pattern of pH-dependent expression [J]. *Mol Cell Biol*, 1997, 17(10): 5960-7.
[96] Fonzi W A. PHR1 and PHR2 of Candida albicans encode putative glycosidases required for proper cross-linking of beta-1,3- and beta-1,6-glucans [J]. *J Bacteriol*, 1999, 181(22): 7070-9.
[97] Baek Y U, Martin S J, Davis D A. Evidence for novel pH-dependent regulation of Candida albicans Rim101, a direct transcriptional repressor of the cell wall beta-glycosidase Phr2 [J]. *Eukaryot Cell*, 2006, 5(9): 1550-9.
[98] Wolf J M, Johnson D J, Chmielewski D, et al. The Candida albicans ESCRT pathway makes Rim101-dependent and -independent contributions to pathogenesis [J]. *Eukaryot Cell*, 2010, 9(8): 1203-15.
[99] Li M, Martin S J, Bruno V M, et al. Candida albicans Rim13p, a protease required for Rim101p processing at acidic and alkaline pHs [J]. *Eukaryot Cell*, 2004, 3(3): 741-51.
[100] Xu W, Smith F J, Jr., Subaran R, et al. Multivesicular body-ESCRT components function in pH response regulation in Saccharomyces cerevisiae and Candida albicans [J]. *Mol Biol Cell*, 2004, 15(12): 5528-37.
[101] Obara K, Kihara A. Signaling events of the Rim101 pathway occur at the plasma membrane in a ubiquitination-dependent manner [J]. *Mol Cell Biol*, 2014, 34(18): 3525-34.
[102] Davis D, Wilson R B, Mitchell A P. RIM101-dependent and-independent pathways govern pH responses in Candida albicans [J]. *Mol Cell Biol*, 2000, 20(3): 971-8.
[103] Saporito-Irwin S M, Birse C E, Sypherd P S, et al. PHR1, a pH-regulated gene of Candida albicans, is required for morphogenesis [J]. *Mol Cell Biol*, 1995, 15(2): 601-13.
[104] Cottier F, Sherrington S, Cockerill S, et al. Remasking of Candida albicans β-Glucan in Response to Environmental pH Is Regulated by Quorum Sensing [J]. *mBio*, 2019, 10(5).
[105] Nobile C J, Solis N, Myers C L, et al. Candida albicans transcription factor Rim101 mediates pathogenic interactions through cell wall functions [J]. *Cell Microbiol*, 2008, 10(11): 2180-96.
[106] Kullas A L, Martin S J, Davis D. Adaptation to environmental pH: integrating the Rim101 and calcineurin signal transduction pathways [J]. *Mol Microbiol*, 2007, 66(4): 858-71.
[107] Jiang L, Xu H, Wei M, et al. Transcriptional expression of PHR2 is positively controlled by the calcium signaling transcription factor Crz1 through its binding motif in the promoter [J]. *Microbiol Spectr*, 2024, 12(1): e0168923.
[108] Moyes D L, Wilson D, Richardson J P, et al. Candidalysin is a fungal peptide toxin critical for mucosal infection [J]. *Nature*, 2016, 532(7597): 64-8.
[109] Citiulo F, Jacobsen I D, Miramón P, et al. Candida albicans scavenges host zinc via Pra1 during endothelial invasion [J]. *PLoS Pathog*, 2012, 8(6): e1002777.
[110] Heilmann C J, Sorgo A G, Mohammadi S, et al. Surface stress induces a conserved cell wall stress response in the pathogenic fungus Candida albicans [J]. *Eukaryot Cell*, 2013, 12(2): 254-64.
[111] Dichtl K, Samantaray S, Wagener J. Cell wall integrity signalling in human pathogenic fungi

[J]. *Cell Microbiol*, 2016, 18(9): 1228-38.

[112] Fuchs B B, Mylonakis E. Our paths might cross: the role of the fungal cell wall integrity pathway in stress response and cross talk with other stress response pathways [J]. *Eukaryot Cell*, 2009, 8(11): 1616-25.

[113] De Munck N, Janssens R, Segers I, et al. Influence of ultra-low oxygen (2%) tension on in-vitro human embryo development [J]. *Hum Reprod*, 2019, 34(2): 228-34.

[114] Walaas G A, Gopalakrishnan S, Bakke I, et al. Physiological hypoxia improves growth and functional differentiation of human intestinal epithelial organoids [J]. *Front Immunol*, 2023, 14: 1095812.

[115] Chen T, Wagner A S, Reynolds T B. When Is It Appropriate to Take Off the Mask? Signaling Pathways That Regulate ß(1,3)-Glucan Exposure in Candida albicans [J]. *Front Fungal Biol*, 2022, 3.

[116] Sonneborn A, Bockmühl D P, Gerads M, et al. Protein kinase A encoded by TPK2 regulates dimorphism of Candida albicans [J]. *Mol Microbiol*, 2000, 35(2): 386-96.

[117] Bockmühl D P, Krishnamurthy S, Gerads M, et al. Distinct and redundant roles of the two protein kinase A isoforms Tpk1p and Tpk2p in morphogenesis and growth of Candida albicans [J]. *Mol Microbiol*, 2001, 42(5): 1243-57.

[118] Sosinska G J, De Groot P W J, Teixeira De Mattos M J, et al. Hypoxic conditions and iron restriction affect the cell-wall proteome of Candida albicans grown under vagina-simulative conditions [J]. *Microbiology (Reading)*, 2008, 154(Pt 2): 510-20.

[119] Klengel T, Liang W J, Chaloupka J, et al. Fungal adenylyl cyclase integrates CO2 sensing with cAMP signaling and virulence [J]. *Curr Biol*, 2005, 15(22): 2021-6.

[120] Hall R A, De Sordi L, Maccallum D M, et al. CO(2) acts as a signalling molecule in populations of the fungal pathogen Candida albicans [J]. *PLoS Pathog*, 2010, 6(11): e1001193.

[121] Dostál J, Blaha J, Hadravová R, et al. Cellular Localization of Carbonic Anhydrase Nce103p in Candida albicans and Candida parapsilosis [J]. *Int J Mol Sci*, 2020, 21(3).

[122] Miwa T, Takagi Y, Shinozaki M, et al. Gpr1, a putative G-protein-coupled receptor, regulates morphogenesis and hypha formation in the pathogenic fungus Candida albicans [J]. *Eukaryot Cell*, 2004, 3(4): 919-31.

[123] Pentland D R, Piper-Brown E, Mühlschlegel F A, et al. Ras signalling in pathogenic yeasts [J]. *Microb Cell*, 2017, 5(2): 63-73.

[124] Avelar G M, Pradhan A, Ma Q, et al. A CO(2) sensing module modulates β-1,3-glucan exposure in Candida albicans [J]. *mBio*, 2024, 15(2): e0189823.

[125] Zhang M, Zhu C, Duan Y, et al. The intrinsically disordered region from PP2C phosphatases functions as a conserved CO(2) sensor [J]. *Nat Cell Biol*, 2022, 24(7): 1029-37.

[126] Lu Y, Su C, Solis N V, et al. Synergistic regulation of hyphal elongation by hypoxia, CO(2), and nutrient conditions controls the virulence of Candida albicans [J]. *Cell Host Microbe*, 2013, 14(5): 499-509.

[127] Chow E W L, Pang L M, Wang Y. From Jekyll to Hyde: The Yeast-Hyphal Transition of Candida albicans [J]. *Pathogens*, 2021, 10(7).

[128] Fan Y, He H, Dong Y, et al. Hyphae-specific genes HGC1, ALS3, HWP1, and ECE1 and relevant signaling pathways in Candida albicans [J]. *Mycopathologia*, 2013, 176(5-6): 329-35.

[129] Synnott J M, Guida A, Mulhern-Haughey S, et al. Regulation of the hypoxic response in Candida albicans [J]. *Eukaryot Cell*, 2010, 9(11): 1734-46.

[130] Sellam A, Van Het Hoog M, Tebbji F, et al. Modeling the transcriptional regulatory network that controls the early hypoxic response in Candida albicans [J]. *Eukaryot Cell*, 2014, 13(5): 675-90.

[131] Ding C, Vidanes G M, Maguire S L, et al. Conserved and divergent roles of Bcr1 and CFEM proteins in Candida parapsilosis and Candida albicans [J]. *PLoS One*, 2011, 6(12): e28151.

[132] Barelle C J, Priest C L, Maccallum D M, et al. Niche-specific regulation of central metabolic pathways in a fungal pathogen [J]. *Cell Microbiol*, 2006, 8(6): 961-71.

[133] Brown A J, Brown G D, Netea M G, et al. Metabolism impacts upon Candida immunogenicity and pathogenicity at multiple levels [J]. *Trends Microbiol*, 2014, 22(11): 614-22.

[134] Baldewijns S, Sillen M, Palmans I, et al. The Role of Fatty Acid Metabolites in Vaginal Health and Disease: Application to Candidiasis [J]. *Front Microbiol*, 2021, 12: 705779.

[135] Vylkova S, Lorenz M C. Modulation of phagosomal pH by Candida albicans promotes hyphal morphogenesis and requires Stp2p, a regulator of amino acid transport [J]. *PLoS Pathog*, 2014, 10(3): e1003995.

[136] Sun Q, Dong B, Yang D, et al. Zcf24, a zinc-finger transcription factor, is required for lactate catabolism and inhibits commensalism in Candida albicans [J]. *Mol Microbiol*, 2023, 119(1): 112-25.

[137] Lagree K, Woolford C A, Huang M Y, et al. Roles of Candida albicans Mig1 and Mig2 in glucose repression, pathogenicity traits, and SNF1 essentiality [J]. *PLoS Genet*, 2020, 16(1): e1008582.

[138] Oliveira-Pacheco J, Alves R, Costa-Barbosa A, et al. The Role of Candida albicans Transcription Factor RLM1 in Response to Carbon Adaptation [J]. *Front Microbiol*, 2018, 9: 1127.

[139] Ramírez-Zavala B, Mottola A, Haubenreißer J, et al. The Snf1-activating kinase Sak1 is a key regulator of metabolic adaptation and in vivo fitness of Candida albicans [J]. *Mol Microbiol*, 2017, 104(6): 989-1007.

[140] Su C, Lu Y, Liu H. N-acetylglucosamine sensing by a GCN5-related N-acetyltransferase induces transcription via chromatin histone acetylation in fungi [J]. *Nat Commun*, 2016, 7: 12916.

[141] Naseem S, Min K, Spitzer D, et al. Regulation of Hyphal Growth and N-Acetylglucosamine Catabolism by Two Transcription Factors in Candida albicans [J]. *Genetics*, 2017, 206(1): 299-314.

[142] Sahoo S, Sharma S, Singh M P, et al. Metabolic and Phenotypic Changes Induced during N-Acetylglucosamine Signalling in the Fungal Pathogen Candida albicans [J]. *Biomedicines*, 2023, 11(7).

[143] Silao F G S, Ljungdahl P O. Amino Acid Sensing and Assimilation by the Fungal Pathogen Candida albicans in the Human Host [J]. *Pathogens*, 2021, 11(1).

[144] Silao F G S, Ward M, Ryman K, et al. Mitochondrial proline catabolism activates Ras1/cAMP/PKA-induced filamentation in Candida albicans [J]. *PLoS Genet*, 2019, 15(2): e1007976.

[145] Williams R B, Lorenz M C. Multiple Alternative Carbon Pathways Combine To Promote

Candida albicans Stress Resistance, Immune Interactions, and Virulence [J]. *mBio*, 2020, 11(1).

[146] Iyer K R, Robbins N, Cowen L E. The role of Candida albicans stress response pathways in antifungal tolerance and resistance [J]. *iScience*, 2022, 25(3): 103953.

[147] Walker L A, Munro C A, De Bruijn I, et al. Stimulation of chitin synthesis rescues Candida albicans from echinocandins [J]. *PLoS Pathog*, 2008, 4(4): e1000040.

[148] Perlin D S. Echinocandin Resistance in Candida [J]. *Clin Infect Dis*, 2015, 61 Suppl 6(Suppl 6): S612-7.

[149] Heredia M Y, Gunasekaran D, Ikeh M a C, et al. Transcriptional regulation of the caspofungin-induced cell wall damage response in Candida albicans [J]. *Curr Genet*, 2020, 66(6): 1059-68.

[150] Xiong K, Su C, Sun Q, et al. Efg1 and Cas5 Orchestrate Cell Wall Damage Response to Caspofungin in Candida albicans [J]. *Antimicrob Agents Chemother*, 2021, 65(2).

[151] Bruno V M, Kalachikov S, Subaran R, et al. Control of the C. albicans cell wall damage response by transcriptional regulator Cas5 [J]. *PLoS Pathog*, 2006, 2(3): e21.

[152] Singh S D, Robbins N, Zaas A K, et al. Hsp90 governs echinocandin resistance in the pathogenic yeast Candida albicans via calcineurin [J]. *PLoS Pathog*, 2009, 5(7): e1000532.

[153] Wheeler R T, Kombe D, Agarwala S D, et al. Dynamic, morphotype-specific Candida albicans beta-glucan exposure during infection and drug treatment [J]. *PLoS Pathog*, 2008, 4(12): e1000227.

[154] Walker L A, Munro C A. Caspofungin Induced Cell Wall Changes of Candida Species Influences Macrophage Interactions [J]. *Front Cell Infect Microbiol*, 2020, 10: 164.

[155] Lee Y, Robbins N, Cowen L E. Molecular mechanisms governing antifungal drug resistance [J]. *NPJ Antimicrob Resist*, 2023, 1(1): 5.

[156] Ene I V, Walker L A, Schiavone M, et al. Cell Wall Remodeling Enzymes Modulate Fungal Cell Wall Elasticity and Osmotic Stress Resistance [J]. *mBio*, 2015, 6(4): e00986.

[157] Taff H T, Mitchell K F, Edward J A, et al. Mechanisms of Candida biofilm drug resistance [J]. *Future Microbiol*, 2013, 8(10): 1325-37.

[158] Nett J, Lincoln L, Marchillo K, et al. Putative role of beta-1,3 glucans in Candida albicans biofilm resistance [J]. *Antimicrob Agents Chemother*, 2007, 51(2): 510-20.

[159] Taff H T, Nett J E, Zarnowski R, et al. A Candida biofilm-induced pathway for matrix glucan delivery: implications for drug resistance [J]. *PLoS Pathog*, 2012, 8(8): e1002848.

[160] Nobile C J, Nett J E, Hernday A D, et al. Biofilm matrix regulation by Candida albicans Zap1 [J]. *PLoS Biol*, 2009, 7(6): e1000133.

[161] Fourie R, Kuloyo O O, Mochochoko B M, et al. Iron at the Centre of Candida albicans Interactions [J]. *Front Cell Infect Microbiol*, 2018, 8: 185.

[162] Pradhan A, Avelar G M, Bain J M, et al. Non-canonical signalling mediates changes in fungal cell wall PAMPs that drive immune evasion [J]. *Nat Commun*, 2019, 10(1): 5315.

[163] Tripathi A, Liverani E, Tsygankov A Y, et al. Iron alters the cell wall composition and intracellular lactate to affect Candida albicans susceptibility to antifungals and host immune response [J]. *J Biol Chem*, 2020, 295(29): 10032-44.

[164] Bai C, Xu X L, Chan F Y, et al. MNN5 encodes an iron-regulated alpha-1,2-mannosyltransferase important for protein glycosylation, cell wall integrity, morphogenesis, and virulence in Candida albicans [J]. *Eukaryot Cell*, 2006, 5(2): 238-47.

[165] Yu Q, Dong Y, Xu N, et al. A novel role of the ferric reductase Cfl1 in cell wall integrity, mitochondrial function, and invasion to host cells in Candida albicans [J]. *FEMS Yeast Res*, 2014, 14(7): 1037-47.

[166] Xu N, Dong Y, Cheng X, et al. Cellular iron homeostasis mediated by the Mrs4-Ccc1-Smf3 pathway is essential for mitochondrial function, morphogenesis and virulence in Candida albicans [J]. *Biochim Biophys Acta*, 2014, 1843(3): 629-39.

[167] Malavia D, Lehtovirta-Morley L E, Alamir O, et al. Zinc Limitation Induces a Hyper-Adherent Goliath Phenotype in Candida albicans [J]. *Front Microbiol*, 2017, 8: 2238.

[168] Kalinina I, Wilson D. Candida albicans Goliath cells pioneer biofilm formation [J]. *mBio*, 2025, 16(9): e0342524.

[169] Henry M, Khouas M, Théberge-Julien G, et al. Manganese homeostasis modulates glucan and chitin unmasking in the opportunistic yeast Candida albicans [J]. *Virulence*, 2025, 16(1): 2569630.

[170] Holt A M, Nett J E. Innate immune response to Candida auris [J]. *Curr Opin Microbiol*, 2024, 80: 102510.

[171] Wang Y, Zou Y, Chen X, et al. Innate immune responses against the fungal pathogen Candida auris [J]. *Nat Commun*, 2022, 13(1): 3553.

[172] Muñoz J F, Gade L, Chow N A, et al. Genomic insights into multidrug-resistance, mating and virulence in Candida auris and related emerging species [J]. *Nat Commun*, 2018, 9(1): 5346.

[173] De Jong A W, Hagen F. Attack, Defend and Persist: How the Fungal Pathogen Candida auris was Able to Emerge Globally in Healthcare Environments [J]. *Mycopathologia*, 2019, 184(3): 353-65.

[174] Yang M, Solis N V, Marshall M, et al. Control of β-glucan exposure by the endo-1,3-glucanase Eng1 in Candida albicans modulates virulence [J]. *PLoS Pathog*, 2022, 18(1): e1010192.

[175] De Assis L J, Bain J M, Liddle C, et al. Nature of β-1,3-Glucan-Exposing Features on Candida albicans Cell Wall and Their Modulation [J]. *mBio*, 2022, 13(6): e0260522.

[176] Dakalbab S, Hamdy R, Holigova P, et al. Uniqueness of Candida auris cell wall in morphogenesis, virulence, resistance, and immune evasion [J]. *Microbiol Res*, 2024, 286: 127797.

[177] Horton M V, Eix E F, Johnson C J, et al. Impact of Micafungin on Candida auris β-glucan Masking and Neutrophil Interactions [J]. *J Infect Dis*, 2024, 230(3): 763-7.

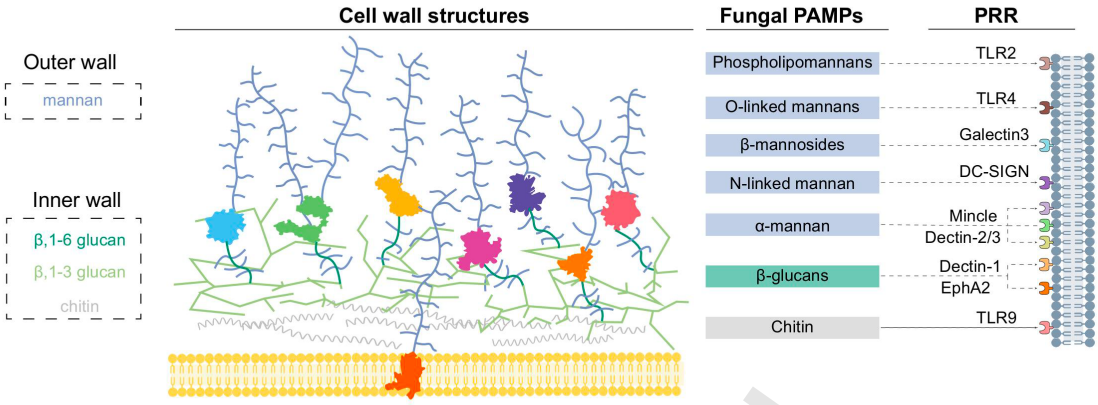

Figure 1. Structural organization of major cell wall components of *C. albicans* and their function as Pathogen-Associated Molecular Patterns (PAMPs) in recognition by host Pattern Recognition Receptors (PRRs).

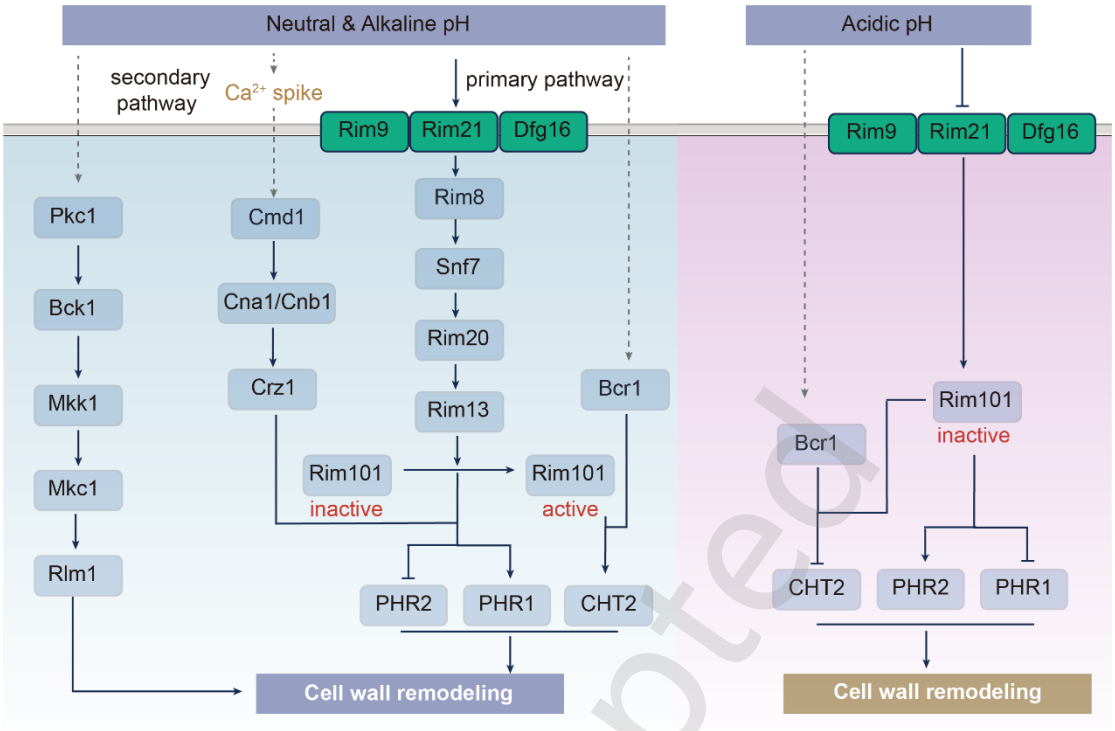

Figure 2. Regulatory mechanisms governing cell wall structural remodeling in response to environmental pH changes in *C. albicans*.

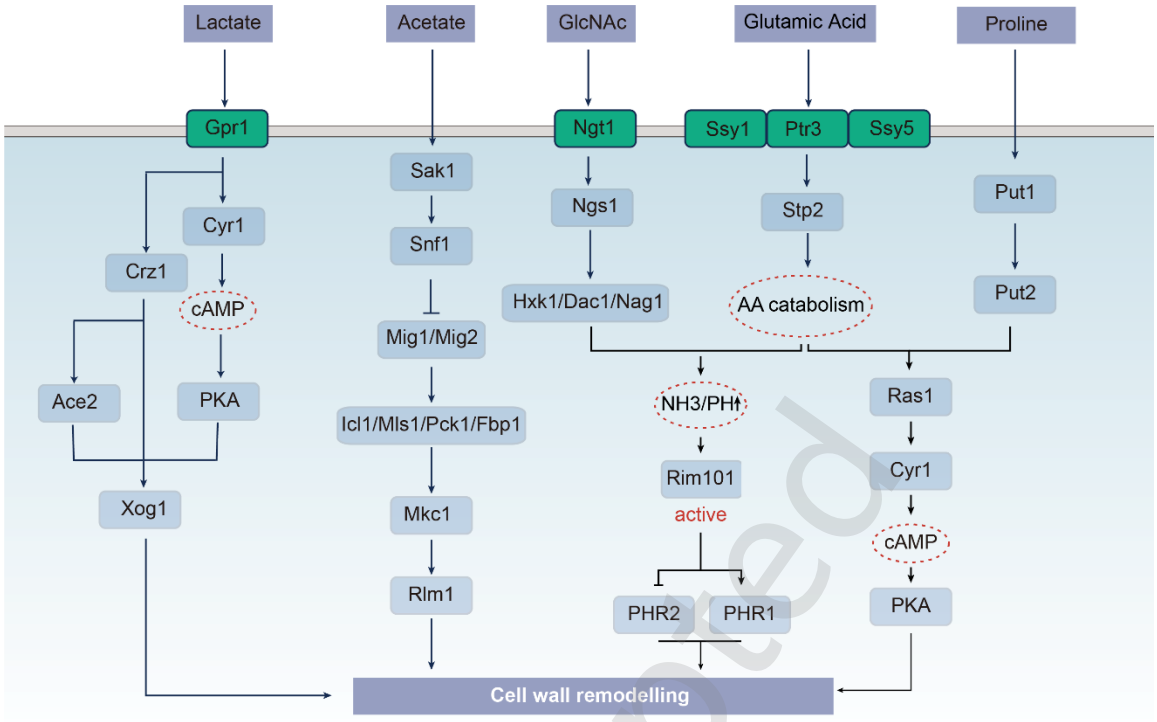

Figure 3. Schematic representation of metabolic pathways regulating *C. albicans* cell wall remodeling through alternative carbon source utilization, including organic acids, GlcNAc, and amino acids.