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**Innate Anti-Candidal Immunity and Evasive Strategies.**

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**Summary**

Candidiasis, an opportunistic infection commonly caused by the polymorphic commensal fungal agent, *Candida albicans* yielding a spectrum of infection from mild superficial infection to invasive disseminated disease. The systemic candidiasis occurs widely among immunocompromised patients with mostly fatal outcomes. *Candida* survived with us from birth to death, predominantly in symbiotic settings on the skin and mucosal surfaces. But in the presence of compromised immune systems from varying causes or when the *Candida* trooped outside its usual confinement, then they become opportunistic and cause severe disease. The resultant systemic spread is expensive to manage, allowing short response time before conceding a mortal score. The systemic candidiasis carries high mortality even in the most advanced settings. Despite extensive research, candidiasis remains a significant health problem globally. The host immune system at various levels uses pattern recognition receptors (PRRs) to identify candidal pathogen-associated molecular patterns (PAMPs). The defense aim at control using barriers, phagocytosis, secretory antimicrobial peptides (AMPs), complements, neutrophil extracellular traps (NETs), and the like. Of note, *Candida* devises a multitude of ways to overcome virtually all the protective strategies of the human host defense. *Candida* evades the host immune system using an array of mechanisms to establish infection. Evasive modalities include proteolytic enzymes, nutrient scavenging, and free radicals' detoxification. Other methods involved concealment of PAMPs through shape shifting, diverting candidal

recognition towards the production of anti-inflammatory cytokines. Here we review some of these host-pathogen interactions to aid the development of immunotherapies.

**Keywords:** *Candida albicans*, candidiasis, phagocytosis, antimicrobial peptides, innate immune response, immune evasion.

**Candidiasis**

Candidiasis is a fungal infection caused by the members of the genus *Candida*. This eukaryotic polymorphic fungal agent survives on mucosal surfaces of vulvo-vagina, gastrointestinal tract, and anorectum of a healthy host. *Candida* caused opportunistic infections of humans as part of the healthy flora but can lead to a life-threatening disease (Tedila et al., 2019). *C. albicans* is the most prevalent fungal pathogen in human mycotic infections. Scientists reported *C. albicans* as the sole etiologic agent in 90% of systemic candidiasis (Kumari et al., 2018).

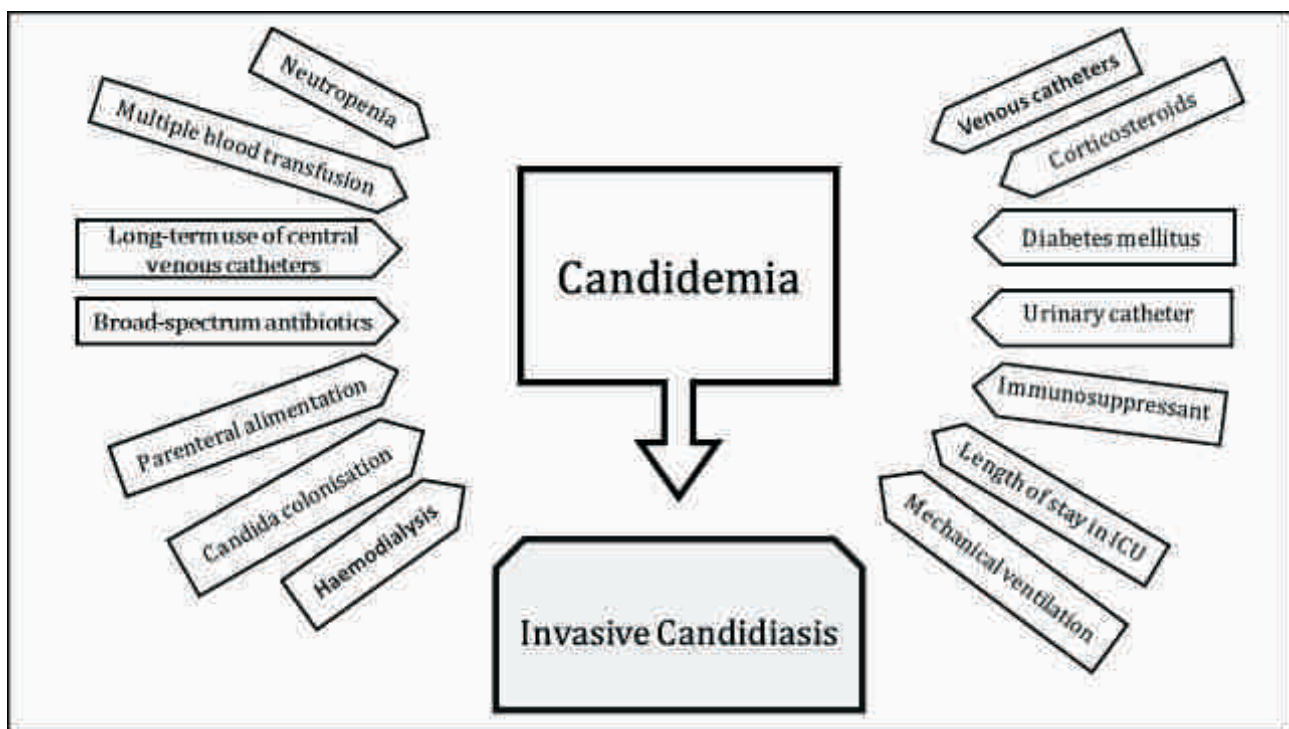
The clinical disease caused by *C. albicans* ranges from muco-cutaneous to systemic candidiasis. Broadly, classified into superficial (oral thrush and vaginitis), cutaneous, subcutaneous, and severe systemic (deep) candidiasis. Ranked based on the extent of the tissue affected and the attending host response that ensures tissue pathology (Bhakt et al., 2018). Subcutaneous, cutaneous, percutaneous, and airborne routes are the portal of entry through exogenous way for *C. albicans* into the host (Walsh and Dixon, 1996). Alternatively, immunosuppression can liberate an endogenous commensal to cause an invasive candidaemia with associated 40% mortality

(Bhakt et al., 2018). In an animal study mortality of 80 – 90% within the first three days resulted from *C. albicans* and *Staphylococcus aureus* (Lilly et al., 2019)

The appearance of the members of the genus *Candida* in the bloodstream is called candidaemia. While widespread established infection with associated pathology in distant organs defines disseminated candidiasis (Vincent et al., 1998b). *C. albicans* can spread in the bloodstream leading to systemic candidiasis, with a resultant fatal outcome that is difficult to diagnose -expensive and not easy to treat clinical state. Half of all invasive candidiasis cultures are negative. Scientist proposes relying on non-culture tests for diagnosis (Clancy and Nguyen, 2018).

Generally, immunosuppression predisposes to invasive candidiasis that's highly fatal (Tedila et al., 2019). Treatment is less promising due to high cost, resistance, and profound associated side effects. However, the human body equipped with natural defense mechanisms against pathogens protects itself by employing innate barriers.

The incidence of this debilitating clinical condition is rising on a global scale (Pfaller and Diekema, 2007). Picazo et al. (2008) demonstrated that post-surgical and immunocompromised patients are at higher risk of disseminated candidemia. Researchers established a relationship of independent risk factors to systemic candidiasis using multiple regression modality (Vincent et al., 1998a), which we depicted in figure 1 below.



**Figure 1: Risk Factors for the Development of Invasive Candidiasis**

**Host Invasion by *C. albicans***

The *C. albicans* are generally acquired at birth when the baby is passing through the birth canal, where they existed as commensals, neonates can also acquire the infection from health workers, an additional risk factor here is the low birth weight (Noori Sanami et al., 2015). The *Candida* species colonize mucosal and epithelial surfaces as part of the commensal relationship with the

host. However, when the immunity is compromised, or the innate barrier is a breach, then the initial colonizing population of *Candida* becomes the source of opportunistic *Candida* (Tyc et al., 2016). The *C. albicans* invade epithelial surface through either receptor-mediated endocytosis or active penetration (Richardson et al., 2018).

*C. albicans* utilize two distinct mechanisms to invade oral epithelium. One is through the production of secreted aspartyl proteinases (SAPs). This protease lyses part of the epithelial surface membrane creating access for the organism, thereby aiding adhesion and colonization (Kumar et al., 2015). Alternatively, candida induces endocytosis through the expression of invasins (Als3 and Ssa1), which now ligates N-cadherin and complexed with septin- 7 (GTP-binding protein). The complex induces microfilaments and pseudopods formation to engulf the Candida (Qin et al., 2016). Mutant strains of Candida lacking Efg1p (transcription factor), Tpk2 (catalytic subunit of protein kinase A) and Cka2 (catalytic subunit of protein kinase CK2) could not invade and damage epithelial cells in the experimental murine animals (Chiang et al., 2007; Lo et al., 1997). It is now clear that these proteins were prerequisites for strains of *C. albicans* to be pathogenic, which serves as part of its virulent factors.

The *C. albicans* secrete proteins of the adhesins and integrin family, for instance, Phosphoglyceratmutase 1 (Gpm1) that recognize specific host proteins like vitronectin and initiate adhesion of the pathogen through integrin  $\alpha\beta 3$  and  $\alpha\beta 5$ -like adhesin on the host epithelial cells thereby facilitating its virulence (Qin et al., 2016). Blocking the genes of these proteins resulted in less epithelial adherence, less cellular damage, and avirulence (Hoyer, 2001, Tsuchimori et al., 2000). The *C. albicans* secrete phospholipases that damage cell membranes and aid direct penetration of the pathogen into the host cells (Naglik et al., 2003; Ibrahim et al., 1995). *C. albicans* cell wall with its constituent complex sugar moieties apart from the structural function of shape, protection, and maintenance of the internal physiologic milieu of the fungus, equips the organism with the ability to withstand harsh conditions, modulate the immune system, and adhere to the host cell (Navarro-García, 2001).

The *C. albicans* exhibit yeast and hyphal forms interchangeably (morphological-shift). The shift leads to the confusion of the immune system by obscuring some of the antigenic determinant present in a pre-transition state, thereby aiding fungal escape and virulence. But restriction of

the fungus into one single form makes it less virulent (Calderone and Fonzi, 2001; Lo et al., 1997). Phenotypic switching of the *C. albicans* growing colonies not only ensures morphological diversity but also expressed a heterogeneity of antigenic phenotype of the fungus that aid host evasion (Calderone and Fonzi, 2001).

### **Immunity to *C. albicans* Infection**

The critical question here is; how does the body defend itself against *C. albicans* infection? A eukaryotic commensal we picked during parturition and lived with us together – “till death do us apart,” yet with the propensity to cause fatal disease whenever opportunity avails. Principally, innate barriers of skin and mucous membranes form the first layer of protection against *C. albicans*. Other intrinsic factors include complement, hydrochloric acid, cathelicidins,  $\beta$  defensins, and cilia. Those, as mentioned earlier, are either fungicidal or disallow candidal wellbeing in those locations. Lactobacillus check the excessive growth of *C. albicans* in the female genital tract principally by interfering with Candida adhesion, as well inhibition of histone deacetylases was postulated to retard fungal growth and adherence to the vaginal epithelium (Parolin et al., 2015).

### **Innate Immunity**

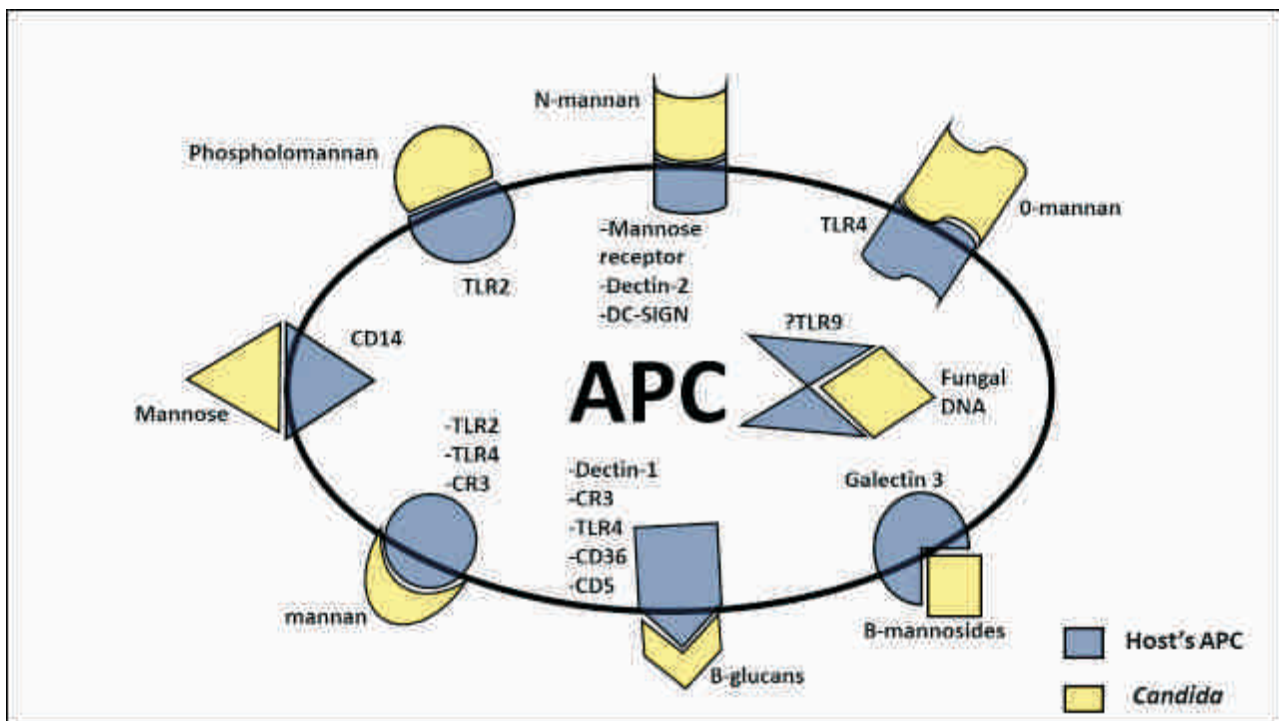
The skin and mucous membranes that line the without and within the human body respectively form a continuous barrier that keeps Candida at bay. Transgression across these barriers by Candida enables it to attain systemic dissemination with fatal outcome (Qin et al., 2016). Phagocytes, macrophages, polymorphonuclear neutrophils (PMN), and dendritic cells are indispensable to candidal immunity (Brown, 2011). Natural killer cells,  $\gamma\delta$  T cells, were also important non-adaptive immune cells in candidiasis; other cells include epithelial and endothelial cells; collectively or individually, they play essential roles toward immunity to *C. albicans* infection (Romani, 2004).

### **C. Albicans Recognition by the immune System**

Host recognizes candidal pathogen through a

robust array of PRRs of the mammalian host, which are either membrane-bound to extracellular or endosomal surfaces or secreted into the body fluids. The PRRs were utilized by the immune cells to identify specific PAMPs to mediate cellular responses through the linkage of intracellular signalling. Recruitment of transcription factors, and production of cytokines to effectively modulate effector immune cells to establish host resistance to the pathogen. The PAMPs, as the name implies, are unique molecular motifs signature that was conserved among pathogens as such recognizes as foreign by the host (Man et al., 2017; Hoffmann and Reichhart, 2002).

The phagocytes (macrophages, neutrophils and dendritic cells) are vital cells that recognize *C. albicans* in the host using their PRRs to identify fungal PAMPs. The PRRs, normally cell wall-associated complex sugar moieties or intracellular molecules like DNA detected using endosomal PRRs. Epithelial cells are also involved in *Candida* recognition (Qin et al., 2016). The complements opsonize the fungus making the pathogen palatable to phagocytes (Brown, 2011). The phagocytes function as APCs and bear PRRs, as shown in figure 2 below.



**Figure 2: A schematic diagram of APC's PRRs and their corresponding Candidal PAMPs**

The phagocytes bear a different combination of PRRs for the recognition of their respective fungal PAMPs, as shown in Table 1 below. The most important here are neutrophils, dendritic cells (DCs), macrophages, and monocytes. The DCs provides a bridge between innate and adaptive immune response since upon phagocytosis, they process the *C. albicans* antigen and present it to CD4+ T cells in lymphoid organs for the initiation of the adaptive immune response. Of note, as introduced above, some of the recognition of *C. albicans* is not done

directly through membrane-bound PRRs. But somewhat indirectly through recognition of soluble PRRs that coat the pathogen and allow membrane-bound complement receptors on phagocytes to recognize them for ultimate engulfment. For example, CR3 that identifies  $\beta$  glucan on *Candida* (Rubin-Bejerano et al., 2007). The Complements opsonize *C. albicans* pathogens for efficient engulfment by phagocytes in patrol (Brown, 2011).

| APCs                   | PRRs   |
|------------------------|--|
| <b>Dendritic cells</b> | CR3<br>DC-SIGN<br>Dectin 1, Dectin 2<br>Fc $\gamma$ R<br>MR<br>TLR2, TLR4, and TLR9          |
| <b>Macrophages</b>     | CR3<br>Dectin 1, Dectin 2<br>Fc $\gamma$ R<br>Galectin 3<br>MR<br>TLR2, TLR4, TLR6, and TLR9 |
| <b>Monocytes</b>       | Dectin 1<br>MR<br>TLR2, TLR4, TLR6, and TLR9   |
| <b>Neutrophils</b>     | CR3<br>Dectin 1<br>Fc $\gamma$ R<br>TLR2 and TLR4  |

**Table 1: Distribution of pattern recognition receptors on Immune cells**

Different immune cells expressed a different combination of PRRs on their cell surface for the recognition of PAMPs. The professional antigen-presenting cells (pAPCs) are more diverse in their PRRs expression (Brown, 2011). Neutrophils and monocytes have limited recognition receptors. The toll-like receptors (TLRs), C-type lectin receptors (CLRs), and nucleotide-binding domain leucine-rich receptors (NLRs) were the main PRRs employed for recognition of *Candida* signature molecular motifs (Netea et al., 2015; Brown, 2011).

Epithelial cells employ ephyrin type-A receptor 2 (EphA2) that recognizes the  $\beta$ -glucans of *Candida*. The EphA2 knockout mice display increased susceptibility to oral candidiasis (Richardson et al., 2018). Epithelial cells also expressed classical PRRs like TLRs and CLRs to recognize candidal PAMPs (Qin et al., 2016).

The CLRs PRRs are composed of a large group

of proteins that recognize foreign molecular motifs, including fungal carbohydrate PAMPs ( $\beta$ -glucans or mannans). The CLRs are widely expressed on myeloid APCs to recognize PAMPs, damage-associated molecular patterns (DAMPs), and tumor-associated molecular patterns (TAMPs). Dectin-1 and Dectin-2 (CLRs) are central to IL-17 function in candidal immunity, a mutation in CARD9 component of IL-17 signalling lead to invasive candidiasis (Dambuza and Brown, 2015). The researchers consider CLRs: Dectin-1, Dectin-2, Dectin-3, Mincle, and mannose receptor (MR) as the most important PRRs for *Candida* PAMPs; they all use CARD9 adaptor molecule for signalling. The CLRs knockout leads to a similar outcome to CARD9 mutation or knockout (Whibley and Gaffen, 2015).

The TLRs were among the first PRRs studied concerning *Candida* recognition. TLR-2 identifies phospholipomannans, and TLR-4

recognizes O-linked mannans while fungal DNA through TLR-9 (Naglik et al., 2017). Signalling along TLRs pathway activates nuclear factor-kappa  $\beta$  (NF- $\kappa$  $\beta$ ) and mitogen-activated protein kinase (MAPK), resulting in expression of pro-inflammatory cytokines: TNF $\alpha$ , IL-6, IL-12, IFN $\alpha$ . Myeloid cells, keratinocytes, and melanocytes secrete these cytokines. TLR knockout or Myd88 adaptor protein deficiency among study mice results in a lack of Th17 immune response, which is the backbone in candidal host defense (Kashem and Kaplan, 2016). In a murine study, the TLR-2 knockouts prove protective of invasive candidiasis, while TLR-4 knockouts made the study animals prone to invasive candidiasis. Seemingly, recognition of *Candida* PAMPs through TLR-1, TLR-6, and TLR9 are non-essential for immunity to *Candida* (Hernández-Santos and Gaffen, 2012).

The NLRs located in the cytoplasm are useful in recognizing fungal chitin, and signalling through NLRs lead to the activation of inflammasome (Naglik et al., 2017). The NLR form part of LRR- and pyrin domain-containing 3 (NLRP3) inflammasome, which upon activation result into the release of IL-18 and IL-1 $\beta$  cytokines. The NLRP3 activation is responsible for discerning opportunistic invasion from mere commensal colonization (Netea et al., 2015), an important factor of Th-17 antifungal immunity (Joly et al., 2012). The NLRP3 deficiency affects pro-inflammatory cytokines production, while NLRP10 knockout mice recorded decrease survival, heighten fungemia. And a deficiency in adaptive proinflammatory immune response (Th1 and Th17) (Joly et al., 2012).

The scavenger receptors (SR) are heterogeneous receptors located on cell membranes that were initially known to recognize oxidized low-density lipoproteins for subsequent endocytosis. Later, scientists discovered that SR is also PRRs, able to recognize PAMPs from bacteria, viruses, and fungi (Canton et al., 2013). The SR expressed by endothelial cells (SREC1, also known as SCARF1) and CD36, both expressed on macrophages and endothelial cells, were shown to be essential PRRs for recognizing  $\beta$  glucans on *C. neoformans* and *C. albicans*. Both SR mentioned act as co-receptors with TLR2 to

activate intracellular signalling that activates NF- $\kappa$  $\beta$  for onward expression of proinflammatory cytokines. The CD36 and SCARF1 are essential for binding the fungal agents while the TLR2 is responsible for signalling. Murine study of knockdown analogues of CD36 and SCARF1 yielded a significant reduction in macrophages activation in response to  $\beta$  glucans recognition on *C. neoformans* and *C. albicans* (Means, 2010; Means et al., 2009).

The complement receptor 3 (CR3/Mac-1/CD11b/CD18) widely distributed on APCs, acts as a PRRs for  $\beta$ -glucan on fungal agents (Winarsih et al., 2019). The NETs formation by PMN and release are dependent on CR3 recognition of  $\beta$ -glucan (Byrd et al., 2013). The CR3 is an opsonic receptor for a complement fragment iC3b in initiating phagocytosis also doubled as an adhesion molecule facilitating leukocyte diapedesis (Paulovičová et al., 2015, Xia and Ross, 1999). Complement Receptor Immunoglobulin (CRIg), expressed on macrophages, and recognizes *C. albicans* opsonized by complements (C3b/iC3b). Infected CRIg knockout mice secrete copious amounts of cytokines with associated shortened survival (Munawara et al., 2017). The CRIg is a member of the immunoglobulin superfamily expressed widely on Kupffer cells. Mice with silenced CRIg are deficient in C3-opsonized pathogens leading to fatality (Helmy et al., 2006).

### The AMPs

The human body widely employed antimicrobial peptides (AMP) as innate factors in converting pathogens. The Amp's exact mechanism of action is still elusive but generally believes to be related to their size, composition, and ionic nature (Baltzer and Brown, 2011). The defensins, cathelicidins, lactoferrin, and histatin 5 have anti-candidal properties, activated through cleavage of their respective precursors (Swidergall and Ernst, 2014).

The cathelicidin (LL-37) possess broader antifungal activity (fungicidal) against *C. albicans*. Expressed vastly by epithelial surfaces induced by *H. pylori* in the stomach, short-chain fatty acids in the colon, and keratinocyte during



inflammation. The LL-37 is also released in huge amounts from secondary granules of neutrophils and mast cells during inflammation (Otte et al., 2009, Turner et al., 1998). The peptide structure of Cathelicidins is conserved among mammals and richly participates in host defense (Otte et al., 2009).

The human cathelicidin hCAP-18, is a 17-kDa peptide stored in neutrophil granules that are subsequently cleaved to 5-kDa peptide, LL-37 with 37 amino acid residues (Ramanathan et al., 2002). Cleaved human cathelicidin LL 37 yields shorter chain RK-31 or KS-30, which has superior antimicrobial activity. But cathelicidins are not fully protective against the spectrum of candidiasis (Richardson et al., 2018). The cathelicidins exhibit amphipathicity, transforming into ion or aqueous channels in the pathogen. Thereby effecting the permeabilization of the candida (Ramanathan et al., 2002). Effectively, it also disrupts the membrane by acting on pathogens membrane lipoproteins which happens after the formation of phagolysosome in phagocytes (López-García et al., 2005).

Defensins like cathelicidin produced by neutrophils and epithelial cells (Trautwein-Weidner et al., 2015). The defensins sense pathogens negatively charged phospholipids and deficiency of cholesterol in pathogens membrane (Yang et al., 2002). Humans have  $\alpha$  and  $\beta$  defensins classified based on disulfide bond and cysteine residues. The  $\alpha$ -defensins are six: four are stored in neutrophils secondary granules named human neutrophil peptide (HNPs 1–4), while human  $\alpha$  defensins 5 and 6 (HD-5 and HD-6) produced by penneth cells. The  $\alpha$  defensins impose exudation of ATP from the Candida. Additionally, it potentiates effector function of mast cells, macrophages, complement, and T cells. The human  $\beta$  defensins (hBDs) made up of eleven members, namely; hBD 1-8, hBD-18, hBD-29, and hBD-31. The  $\beta$  defensins positively charged interact with negatively charged surfaces of candida to induce the formation of pores, thereby promoting leakage of fungal cytosolic content also acts as a chemoattractant (Polesello et al., 2017).

### **The APCs in *C. albicans* infection**

Dendritic cells, macrophages, and B cells were the famous pAPCs. The DCs ingest both the morphological forms of the Candida in murine experimental studies. The internalization of the yeast is associated with good immunity. Through the production of pro-inflammatory Th1 cytokine, IL-12. Ingestion of multicellular hyphal forms leads to the production of anti-inflammatory Th2 cytokine that is IL-4, and reciprocal inhibition of IL-12. Subsequently provides an escape of the hyphae from the phagosome (d'Ostiani et al., 2000).

The APCs internalized their encountered antigen through phagocytosis or pinocytosis. The internalized antigen digested through enzymatic processes. The product of this degradation is then mounted onto the MHC class II molecule to present to CD4<sup>+</sup> T cells. Upon recognition, co-stimulation required through ligation of B7.1 and B7.2 molecules. Secondary to this interaction of T cell and APC, the latter will now secrete cytokines to complete the activation of the T cell (Newman and Holly, 2001). Successful activation of the T cell will lead to a specific T cell response, as described above. The outline mechanism describes the role of DCs in bridging innate and adaptive immune responses during candidiasis.

Dendritic cells: are the major APCs in candidiasis. They use MR, TLR4, and DC-SIGN to recognize  $\alpha$  linked mannose residues on the cell wall of *C. albicans*. Recognition through these receptors results in DCs maturation and activation of cell-mediated immunity. The DCs utilize dectin-2 in conjunction with FC $\gamma$ R to recognize mannan moieties on *C. albicans* hyphal cells to initiate intracellular signalling. DCs dectin-1 and CR3 recognize  $\beta$ -glucans present at the budding scar of *C. albicans* or released in circulation in times of candidaemia. The interaction results in the activation of cell-mediated anti-candidal immune responses. Recognition of *C. albicans* antigens by DCs dictates the type of immune response to be activated (Netea et al., 2008).

Apart from their role in recognizing PAMPs, PRRs play a significant role in mediating

phagocytosis of *C. albicans* pathogens. The PRRs like MR, dendritic cell-specific intracellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), Dectin-1, and SCARF1 facilitate fungal phagocytic uptake. Additionally, TLRs influence engulfment of the fungus even though not formally classified as phagocytic receptors (Brown, 2011). Griffin and his Colleagues in 1975 describe the classical zipper-type phagocytosis, in which we now understand as receptor-ligand (PRRs and PAMPs) reaction (Rittig et al., 1998).

The DCs are classified as the best APCs in *C. albicans* infection as they can process and present candidal antigen with subsequent priming of T cells. The DCs engulf *C. albicans* using different types of phagocytosis. They use the conventional zipper-type mechanism to engulf the hyphal morphology of *Candida*, yielding anti-inflammatory TH2 outcomes. The coiling mechanism deployed in response to yeast forms leads to the induction of pro-inflammatory Th1 response (d'Ostiani et al., 2000).

Phagosome, a compartmentalized organelle, bears chemical and physiological features of the cell membrane bilayer. But progressively undergoes systematic maturation by acquiring features of the endocytic pathway, this depicts its maturation. Phagosomal maturation is associated with loss and acquisition of various makers; more important here are the rab family proteins. The phagosome merges with the lysosome to form a phagolysosome. The lysozyme contributes acid and degradative enzymes to the newly formed compartment (Desjardins et al., 1994). The acidity and the enzymes acquired from the lysozyme aid degradation of the engulfed *Candida* (Tjelle et al., 2000; Tjelle et al., 1998).

**Macrophages:** Macrophages are another group of pAPCs that process and present antigen to T cells to aid cell-mediated immune response. But in candidiasis, macrophage's main function is mostly innate response involving the engulfing and killing of the invading fungus. Macrophages have not proved themselves effective in curtailing candidal infection as the pathogen deploys multiple mechanisms to evade these

immune cells (Romani, 2004) successfully.

**Neutrophils:** Neutrophils are the first group of immune cells to be recruited to the site of inflammation, produced in copious numbers to promote inflammation. They represent the largest population of white blood cells. The PMNs are the cardinal cells in immunity to *C. albicans*, being potent phagocytic cells, able to produce several AMPs, inflammatory cytokines, and NETs (Brown, 2011). The PMNs utilize CR3 to recognize opsonized *Candida* while they deploy Fc $\gamma$ Rs for the recognition of unopsonized *Candida* (Netea et al., 2015). The deficiency of PMNs from different conditions is associated with systemic candidiasis that is often fatal (Polesello et al., 2017).

### **Evasion of the Immune System by the *C. albicans***

In the evolutionary trend, as the defense system of the host becomes more elaborate and sophisticated, complementary escape strategies of the invading agent also evolve, be it cancer or pathogen. Pathogens devise necessary structures and mechanisms to evade the host defense; *C. albicans* is not an exception in this regard. The *Candida* evades recognition, complement activation, phagocytosis, phagosome maturation, and phagosomal lysis. Activation of anti-inflammatory mechanisms which allow for candidal survival within the host is another mechanism of evasion.

**Evasion of biological barriers:** As highlighted above, the first opportunity by which the fungus gets into the circulation, be it mechanical or chemical, which may involve one or more of the following factors outlined in figure 1. The aforementioned provides the first candidal circumvention of the immune system's mechanical innate barrier (Vincent et al., 1998b). The innate immune system is crucial in keeping a check on *C. albicans* (commensal). Candidal escape of the biological barriers exposed the host to candidaemia and subsequent invasive candidiasis. Adaptive immune response requires a longer time to be effective because of which host relies solely on phagocytes and AMPs as the key to this immunity.



Evasion of antimicrobial peptide: *C. albicans* devise multiple strategies to counteract AMPs. It secretes Msb2 to inactivate cathelicidins and defensins also to stabilize the candidal cell wall. Again *C. albicans* use polyamine efflux transporter Flu1 to pump out AMPs out of the candida (Dühring et al., 2015). *C. albicans* in the oral cavity produce Sap9 that cleaves salivary histatin-5, thereby rendering it ineffective in its anti-candidal activity. The histatin 5 is prerequisite in maintaining the commensal relationship between the candida and the host in the salivary gland. Its absence leads to opportunistic infection by *C. albicans* (Meiller et al., 2009).

Free radical detoxification: Phagocytes generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). The reactive species aid fungal lysis in phagosomes. The *C. albicans* was shown to detoxify the free radicals that are formed through the host expression of Hog1, Cap1, and Yap1 (Brown et al., 2009). The candida species expressed enzymes with antioxidant and immunodominant functions. Which include catalases, superoxide dismutases, peroxidases, and glutathione reductases. These enzymes neutralize reactive oxygen and nitrogen free radicals in the phagolysosome (Cuéllar-Cruz et al., 2014).

Evasion of phagosomal maturation: Phagosomal maturation is requisite to candidal killing. Virulent candida displays immune evasion compared to avirulent strain. A study found statistically significant reduction of late phagosomal markers among virulent candida. The markers studied include; F-actin, lysobisphosphatidic acid, cathepsin D, LAMP-1, acidity, V ATPase, and nitric oxide in association (Fernández-Arenas et al., 2009). Above signifies the maintenance of the phagosome in early phenotype, hampers phagosome-lysosome fusion. Thereby preventing acidification and enzymatic degradation of phagosome content. The effect of this leads to the inability to kill the Candida effectively. The result is an escape of the pathogen from the immune system. Delay in processes involved in killing the Candida will inadvertently buy more time for the organism to grow into the hyphal form, which eventually

ruptures the phagosome with a resultant escape into the cytoplasm (Wilson et al., 2016; Fernández-Arenas et al., 2009).

Evasion of the complement system: *C. albicans* employ two main mechanisms to evade the complement system. Firstly, it produces aspartyl proteases enzymes that digest the C3b, C4b, and C5 complement factors, thereby abolishing opsonization. Secondly, it acquires complement regulators fH, FKL-1, plasminogen, vitronectin, and C4BP. In sum, lead to degradation of C3 and C5 convertases and inactivation of C3b and C4b. The cumulative effect is the loss of all three pathways of complement activation, giving a good blanket cover to the fungus to continue its growth unopposed (Dühring et al., 2015; Speth et al., 2008).

Evasion of recognition by the phagocytes: Dectin-1 recognizes and binds  $\beta$ -glucans present on the yeast forms of the candida. Hyphal growth conceals  $\beta$ -glucans, which are needed to initiate internalization. Concealment happens due to scarring at the site of budding. However, this study shows that the  $\beta$ -glucans concealed by  $\beta$  glucans are important for activation of APC's phagocytosis, which in association with TLRs, induce intracellular signalling. As adaptor proteins recruited, then follows the activation of transcription of Th1 pro-inflammatory cytokines. Hence,  $\beta$ -glucans concealments dampen down phagocytes, in turn, are less aggressive against the fungal invasion (Dühring et al., 2015; Gantner et al., 2005). Hyphal formation induces macrophage lysis through pyroptosis and cell membrane rupture (Wilson et al., 2016).

Evasion of the inflammatory pathways: Additionally, *C. albicans* can target important PRRs on the host, for example, DC-SIGN, Fc $\gamma$ R, CR3, and TLR2 with the resultant diversion of the immune system towards anti-inflammatory response to its presence through the production of IL-10. Also, IL-10 and IL-4 polymorphisms prone hosts to candidiasis (Brown, 2011).

Other molecules involved in candidal host evasion: The Mannans, PAMPs of Candida shield  $\beta$  1,3-glucans against recognition by the

host Dectin-1 (Dühring et al., 2015), while the transferrin and Pra 1 receptors function as scavengers to overpower host nutritional immunity to iron and zinc by the host respectively. The *Candida* species form protective asteroid bodies that trap IgGs and IgMs. While Rod A hamper NETs formation in neutrophils and candidal production of biofilm provides resistance to neutrophil attack by-passing ROS, ensuring immune escape (Hernández-Chávez et al., 2017).

### Conclusion

Candidiasis being a prevalent infection was researched extensively globally with mild to severe presentation, which depends on the immune status of the host in most cases. Both non-adaptive and adaptive immune responses struggle to contain candidiasis. With a non-adaptive response trying to curtail the *Candida* adventurism from symbiotic relation to pathogenic one. The mucosal membrane barriers, Phagocytes, AMPs, innate cytokines, NETS are the key arsenal of the innate immune response deployed to institute host resistance to *Candida*. Whereas, candidal pathogens circumvent developed immune defenses using different evading mechanisms to aid their survival. Comprehending candidal evasive strategies is basic to immunotherapy design.

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