


Mucocutaneous Defense Mechanisms against Candida Infection

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ABSTRACT

Candida albicans is a commensal organism that can may become invasive and fatal under certain circumstances. Several genetic variations in the human genome towards susceptibility to *Candida* infections have been identified. There are a number of genes associated with *Candida* virulence factors, host environment, and immune response. C-type lectin receptors (CLRs) are characterized by leucine-rich and nucleotide-binding domains that can detect intracellular signals through various types of cytoplasmic domains. CLRs are family of PRRs that bind glycan through recognition of extracellular carbohydrate and mediate intracellular signaling through various type of cellular domains, resulting in a decrease of neutrophils and facilitating the occurrence of fungal infections. This study review the genetic determinant of defense mechanisms and immune deficiencies against *Candida* infection.

Keywords: Adaptive immunity, *Candida*, defense mechanism, innate immunity, mucocutaneous.

ABSTRAK

Candida albicans adalah organisme komensal yang dapat menjadi invasif dan fatal dalam keadaan tertentu. Ada beberapa variasi genetik dalam genom manusia yang telah diidentifikasi memiliki kerentanan terhadap infeksi *Candida*. Terdapat sejumlah gen yang berhubungan dengan faktor virulensi *Candida*, lingkungan inang, dan respons imun tubuh. *C-type lectin receptors* (CLR) ditandai dengan *domain* pengikat nukleotida dan kaya leusin yang dapat mendeteksi sinyal intraseluler melalui berbagai jenis domain sitoplasma. CLR adalah keluarga PRR yang mengikat glikan melalui pengenalan karbohidrat ekstraseluler dan memediasi sinyal intraseluler melalui berbagai jenis domain seluler, yang mengakibatkan penurunan neutrofil dan memfasilitasi terjadinya infeksi jamur. Studi ini meninjau faktor penentu genetik mekanisme pertahanan dan defisiensi imun terhadap infeksi *Candida*. **Adelia Wuri Pramudita, Harijono Kariosentono, Annisa Marsha Evanti, Zilpa Widyastuti. Mekanisme Pertahanan Mukokutan terhadap Infeksi *Candida*.**

Kata Kunci: Imunitas adaptif, *Candida,* mekanisme pertahanan, imunitas bawaan, mukosa.

INTRODUCTION

Candida is a commensal organism in the skin and mucous membranes. *Candida* can become invasive and fatal under certain circumstances in case of neutropenia, pancreatitis, renal insufficiency, human immunodeficiency virus (HIV) infection, systemic glucocorticosteroid, or antibiotic treatment, patients with invasive medical devices, total parenteral nutrition, and major abdominal surgery.[1]

The prevalence of *Candida* infection differs by age group. In adult patients aged 18 years or older, *Candida albicans* (*C. albicans*) is the most common cause, while in neonates, *C. albicans* and *C. parapsilosis* are the most common species. Both species can cause candidemia associated with catheter use in neonates.[2] *Candida sp.* is most commonly isolated from the oral cavity, vulvovaginal area, urinary tract, and gastrointestinal tract in approximately 31%–55% of healthy individuals, with *C. albicans* accounting for 70%–80% of clinical isolates.[3]

The frequency of *Candida* infection increases in HIV-positive patients, diabetes, and immunosuppressive conditions, as well as patients with occlusive conditions, moisture, skin barrier dysfunction, hormonal imbalance, and irrational use of antibiotics. Diseases caused by *Candida* mucocutaneous infection include vulvovaginal candidiasis, oropharyngeal candidiasis in the form of acute pseudomembranous candidiasis, chronic atrophic stomatitis, angular cheilitis (perleche), chronic hyperplastic candidiasis, and midline glossitis (acute atrophic stomatitis), while cutaneous candidiasis includes generalized cutaneous candidiasis, intertrigo, interdigitalis blastomycetica erosion, *Candida* folliculitis, and chronic mucocutaneous candidiasis.[4]

Mucocutaneous invasion occurs if there is dysfunction of the skin-mucosa barrier or a decrease in immunity resulting in increased growth of normal flora. Dry, intact skin is a potent defense mechanism against fungal invasion, whereas increased epidermal hydration may decrease resistance against *Candida* invasion.[4] These fungal infections can occur due to individual immunity imbalances, which can be caused by congenital or acquired immunodeficiencies.[2] Depression

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of T lymphocytes or neutrophil-mediated immunity can result in fungal growth and invasion.[5] Recognition of host immunity to *Candida* involves non-specific and specific immune responses.[6]

DISCUSSION

Pathogenesis of Candidiasis

Candida albicans, as a commensal organism, can turn into a pathogen related to candida virulence factors in the form of adhesion, invasion and cell damage by secreting hydrolase enzymes in the form of proteases, phospholipases and lipases that can damage cell membranes and cell organelles. The virulence is influenced by the site of mucosal or systemic infection, the stage of infection, and the natural host responses. Enzymes synthesized by Candida, secreted as aspartyl proteinases (SAP), determine the virulence factors. SAP of *C. albicans* consists of 10 isoenzymes (SAP 1 to 10). SAP 1-3 play an important role for superficial infections, including in the mucosa and skin, while SAP 4-6 are important for systemic infections.[2]

Candida albicans invasion is mediated by two processes, namely endocytosis and active penetration. Endocytosis is performed by host cells, while active penetration by candida is mediated by hyphal extension and production of hydrolytic enzyme factors such as aspartic proteinase. This process results in invasion and induction of host cell damage.[6] Hyphae formation promotes invasion of endothelial and epithelial tissues and allows avoidance of macrophage action.[4] The mechanism of *C. albicans* to resist the immune system is through various means, including yeast to hyphae phase transition, decreased expression of epithelial toll-like receptor 4 (TLR4), refuge from fungal component recognition, inhibition and degradation of the complement system, inhibition of phagolysosome formation, and modulation of T-cell function.[7] *Candida sp.* also could invade the intestinal tract through anastomotic leakage after procedures, which cause deeper local infection or candidemia and lead to secondary spreading infections to the lungs, liver, spleen, kidneys, bones, or eyes.[8]

Innate Immune Responses against *Candida* Infection

The innate immune response is immediately activated when the body recognizes the microbes; this response plays a role in controlling fungal invasion and preventing disease. The interaction between *Candida sp.* and innate immune cells are visualized in the **Figure**.

Factors related to innate immunity against *Candida* were:

A. Epithelial Cells

Epithelial cells separate the host from the environment and then provide the first initial defense against pathogens. Initially, epithelial cells were only thought to be a physical barrier that prevented infections. Recently, epithelial cells are known to also provide anti-microbial activity and respond actively to pathogens. The release of inflammatory mediators from epithelial cells is an important step in protection, including the recruitment of proinflammatory leukocytes and the production of host defense peptide (HDP). HDP release plays an important role in

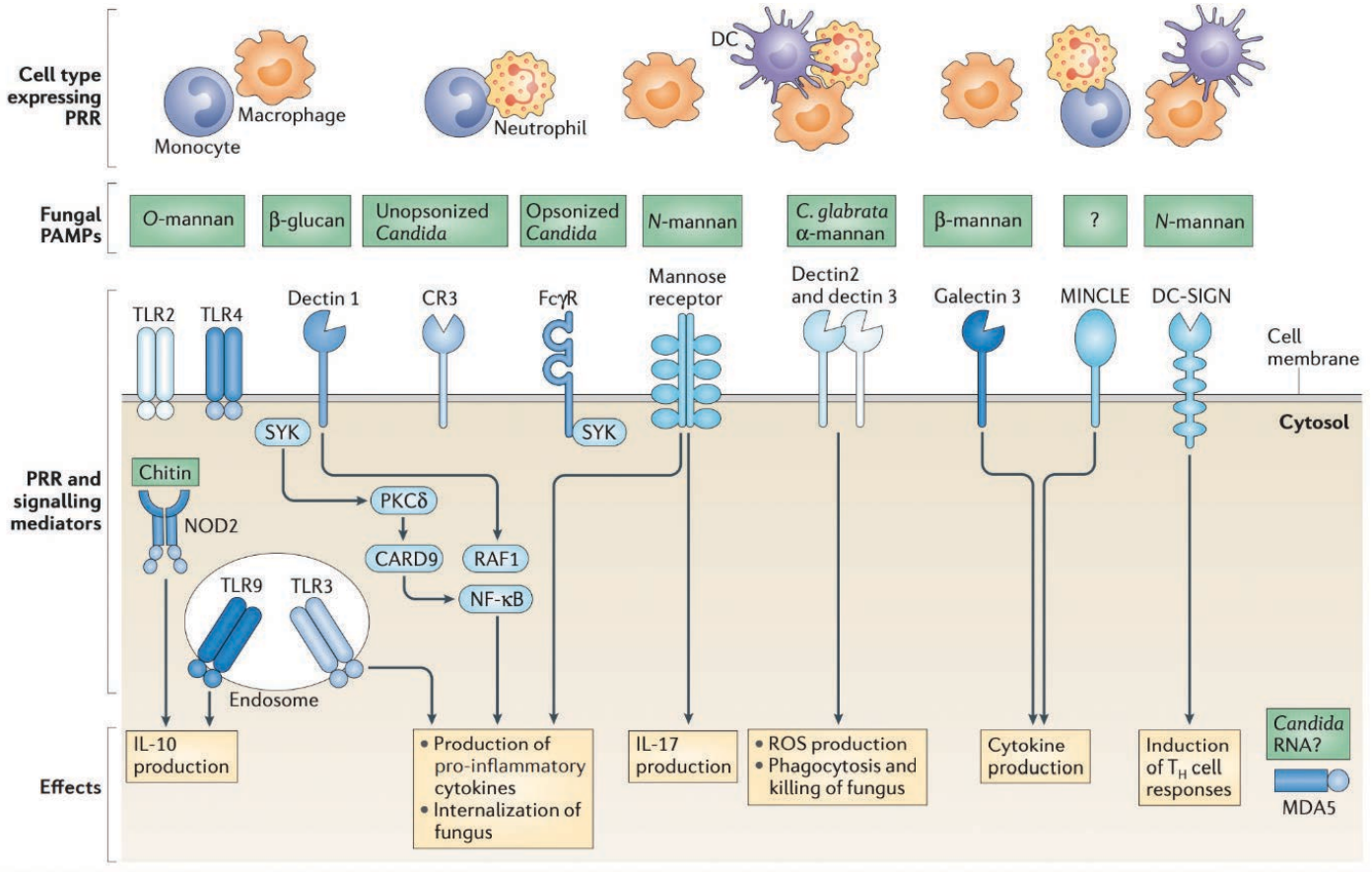

Figure. The recognition of *Candida sp.* by innate immune cells.[1]


regulating non-specific immune responses by enhancing direct and indirect chemotaxis processes. The main types of HDPs in the human oral cavity are defensins, catechins, and histamine. Defensins are found in the inflamed mucosa of the cheeks, gums, tongue, and salivary glands. Cathelicidin has an intracellular target, namely the mitochondria of microorganisms.[9,10]

B. Neutrophils

Neutrophil recruitment is required for a rapid response within 4-8 hours when the body fights fungal pathogens such as *C.* albicans.[11] Neutrophils are able to phagocytize *Candida* blastospores, then fungal hyphae trigger neutrophil extracellular traps (NETs) release. Interleukin-1 (IL-1) on the epithelium bound to the IL-1 receptor spurs an inflammatory response, including the release of HDP. *C. albicans* invasion induces a strong antifungal response in epithelial cells by stimulating proinflammatory cytokines and chemokines release that have a role in recruiting leukocytes. Proinflammatory cytokines that play a role include IL-16, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF) as well as chemokine (C-X-C motif) ligand 8 (CXCL8/ IL-8), chemokine (C-C motif) ligand 20 (CCL20), and regulated upon activation, normal T cell expressed and presumably secreted (RANTES). Epithelial cytokines and chemokines play a major role in host defense against fungal invasion, proving that fungal infection can be controlled on mucosal surfaces.[10]

C. Stromal Cells

The avascular epidermal layer is a horn layer structure composed of keratinocytes, keratin, and hydrophobic lipids. This layer provides a physical barrier to pathogens containing antimicrobials and anti–*Candida* peptides, namely β–defensins and cathelicidin, which are released by keratinocytes as a response against infection or colonization. Additionally, deficiency of ceramide synthase 3 (component of stratum corneum) can facilitate *C. albicans* infection.[12]

D. PPR for *Candida*

Candida is recognized by the immune system by identifying PAMPs, which are common to various types of fungi. Different from antigens, PAMPs are not specific to a particular *Candida sp.* Microbial PAMPs are recognized by the host PRR so that the fungal component can be rapidly recognized. The following is a list of *Candida* PAMPs and the PRRs that recognize them **(Table 1).**[6] Immune cells that express PRR, such as monocytes, macrophages, neutrophils, and dendritic cells, will recognize *Candida* cell PAMPs. The interaction between PRR-expressing immune cells and PAMPs from *Candida* cells will activate intracellular signaling mediators and produce varied immune responses, such as the production of proinflammatory cytokines, reactive oxygen species (ROS), induction of T helper cell responses, and internalization of *Candida* cells.[1]

E. Toll-Like Receptors (TLR)

Some TLRs could recognize *C. albicans* polysaccharides in the cell wall, including TLR2, which recognizes phospholipomannan, and TLR4, which recognizes O-linked mannans. Activation of TLRs by their ligands triggers intracellular signaling pathways, e.g., MAPK and NF-kB, resulting in the transcription and secretion of TNFα, IL–6, and IFN type 1. Toll-like receptors are differentially expressed by various cell types, including natural killer (NK) cells, melanocytes, dendritic cells, and macrophages, and can cooperate with C-type lectins to promote the production of IL-1β, TNF-α, and IL-12.[12]

F. C-type Lectin Receptors (CLRs)

C-type lectin receptors (CLRs) include a group of receptors that bind glycan through recognition of extracellular carbohydrate and mediate intracellular signals through various types of cytoplasmic domains. The most frequently studied CLRs include Dectin-1 which can recognize β-glucan from the cell wall of fungi such as *C. albicans*. Signals from Dectin-1 activate cells by the SYK–dependent pathway, thus forming the caspase recruitment domain family member 9-B-cell lymphoma 10-mucosa-associated lymphoid tissue lymphoma translocation protein 1 (CARD9-BCL10-MALT1) trimer and activation of NF-kB. This mechanism leads to proinflammatory cytokines transcription,

Table 1. Pattern recognition receptors (PPRs) against *Candida*.[6]

PRR	Location	Molecular Recognition	Response against *Candida*
TLR			
TLR1/2	Superficial	Zymosan/ β-glucans	Maybe
TLR2	Superficial	Phospholipomannan; zymosan	Yes
TLR2/6	Superficial	Zymosan/ β-glucans	Maybe
TLR3	Endosomal	dsRNA	Maybe
TLR4	Superficial/ cytoplasmic	O-linked mannan	Yes
TLR9	Endosomal	Fungal DNA not methylated CpG	Yes
C-type lectins			
Dectin-1	Superficial	β-1, 3 glucan; mannan; zymosan	Yes
Dectin-2/3	Superficial	Mannan	Yes
Mannose receptor	Superficial	N-linked mannan; N-acetylglucosamine	Yes
Mincle	Superficial	Mannan	Maybe
DC-SIGN	Superficial	N-linked mannose structure	Maybe
Galectins	cytoplasmic/ nucleus; extracellular	β-1,2 mannoside	Maybe
NLR			
NLRP3	Cytoplasmic	Zymosan/ β-glucans	Yes
NLRC4	Cytoplasmic	Zymosan/ β-glucans	Yes

including IL-1β, IL-6, and IL-12. Some of *C. albicans* species can increase cell wall chitin production thereby decreasing the availability of fungal cell wall β-glucan to be recognized by Dectin-1.[12]

G. Nod-like Receptors (NLR)

Nod-like Receptors (NLR) are a family of intracellular PRRs characterized by leucine-rich and nucleotide-binding domains that can detect PAMPs presented in the cell cytoplasm. Nod-like Receptors are commonly associated with two other proteins, apoptosis-associated speck-like protein containing a CARD (ASC) and procaspase-1, which then form a large multimeric protein complex called the inflamasome. *C. albicans* can activate inflammasomes namely NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) and NLR family CARD domain-containing protein 4 (NLRC4) resulting in IL-1β production.[6] Caspase-1 and ASC are important in defense against *Candida* through expression of IL-1β and IL-18 and induction of Th1 and Th17 antifungal responses.[11]

H. Skin Nerves

Neuronal activation by *C. albicans* increases the secretion of calcitonin gene related peptide (CGRP). Calcitonin gene related peptide has antifungal properties in vitro acting on keratinocyte cells to increase proliferation and in vivo can increase the secretion of interleukin-23 (IL-23).[12]

I. Macrophages

Macrophages release inflammatory cytokines and chemokines that can recruit other immune cells to the site of infection. Previous animal studies with macrophage depletion showed increased fungal proliferation in tissues and increased mortality. Macrophages can recognize and phagocytose nonopsonized *Candida* via TLRs and cytotoxic T cells as well as opsonized *Candida* via complement receptor 3 (CR3) and fragment crystallizable receptor (FcR). Macrophage phagosomes follow the endocytic maturation pathway, and cathepsin D activity is increased in phagolysosomes with an acidic pH. M1 macrophage synthesizes reactive nitrogen species (RNS) and nitric oxide to destroy *Candida* and secrete TNFα, chemokines CXCL9 and CXCL10. M2 macrophage expresses a higher level of mannose receptor (CD206) thus enhancing *Candida* phagocytosis.[6]

Adaptive Immune Response against Candidiasis

Adaptive immune responses can be divided into cell-mediated immunity and humoral immunity. In humans, Th17 cells are the most important mediators of antifungal barrier immunity. Stimulation of naive CD4+ T cells with *C. albicans* can induce clonal T lymphocytes and IL-1β-dependent production of IL-17 and IFN-γ. Memory T cell responses to *C. albicans* show functional heterogenicity.[12–14]

A. Cell-Mediated Immunity

T–lymphocytes are a major part of adaptive immune response against *C. albicans* infection acting directly and indirectly to control fungal proliferation. Both T–helper cells (CD4+) and cytotoxic T–cells (CD8+) have a role in antifungal immunity and controlled by the dendritic cell population. The initial mechanism of adaptive immune response occurs through the presentation of fungal antigens to naive CD4+ T–cells by dendritic cells, resulting in a predominantly T–helper cells response at the mucosal membrane. CD4+ T–cells have no direct cytolytic activity, but still have an important part in the cellular adaptive response against fungal infection. The significance of the T–helper cellular response driving protective immunity against *C. albicans* was evidenced as increased prevalence of oropharyngeal candidiasis in HIV/AIDS patients. The Th1 response was historically thought to be the dominant defensive cellular response against *C. albicans*, which affecting in eradication of the fungus from the oral cavity and gut. Nevertheless, the Th17 response is currently shown to contribute more to the protection of systemic *Candida* infections.[15]

B. Humoral Immunity

The endogenous antibody response against infection of *C. albicans* in humans is thought to play a minor role in immune protection to the fungus and was considered less effective than the cellular response (T-helper 17/T-helper 1). Mannoproteins with O- and N-linked mannose polysaccharide complexes are integral components of the *C. albicans*

Table 2. Primary immunodeficiency associated with susceptibility to candidiasis.[1]

Affected Genes	Main Symptoms	Immunity Defects
STAT1	Chronic mucocutaneous candidiasis, hypothyroidism, esophageal cancer	Decrease of IFN-γ, IL-17 and IL-22 production
STAT3	Hyper-IgE serum, *Candida*, and staphylococcal infections	Decrease of IFN-γ, IL-17 and IL-22 production
DOCK8	Hyper-IgE serum, *Candida*, and staphylococcal infections	Impaired T cell activation, decrease of IFN-γ, IL-17 and IL-22 production
TYK2	Hyper-IgE serum, *Candida*, and staphylococcal infections	Impaired cytokine signalling
IL-17RA	Chronic mucocutaneous candidiasis	Function loss of IL-17RA
IL-17F	Chronic mucocutaneous candidiasis	Function loss of IL-17F
CARD9	Mucosal and disseminated *Candida* infections	Decrease of IL-17 production
IL-12Rβ1	Salmonella, mycobacterium and *Candida* infections	Function loss of IL-12 and IL-23 receptor, Decrease of IFN-γ and IL-17 production
AIRE	Chronic mucocutaneous candidiasis, adrenal insufficiency, hypoparathyroidism	Impaired negative selection of thymus and autoreactive T cells, antibodies to IL-17 and IL-22


cell wall and major targets of anti–*Candida* antibodies. The binding of antibodies to cell surface components of infecting the fungi can inhibit the biological functions of fungi. Antibody protection to *C. albicans* is not limited to cell surface molecules. Antibody–mediated inhibition of SAP activity enhances protection against vaginal candidiasis in mice, whereas the antibodies specific to heat shock protein 90 (Hsp90) of *C. albicans* protect against systemic candidiasis.[15]

Immunodeficiency Associated with Susceptibility to Candidiasis

Conditions that may facilitate fungal invasion include congenital and acquired immunodeficiencies. Congenital defects in granulocyte function such as myeloperoxidase deficiency facilitate *Candida* infection. Immune defects due to iatrogenic or natural causes such as the use of chemotherapy in cancer patients result in a decrease of neutrophils, facilitating the occurrence of fungal infections.[2] Several genetic variations of human genome have been identified as having susceptibility against *Candida* infection. Genetic determinant of primary immunodeficiency may lead to chronic mucocutaneous candidiasis and gene polymorphisms associated with susceptibility to systemic infections have been reported (**Table 2**).[1] Various immune response defects against *C. albicans* in PRR (especially CLR) may deliver in susceptibility to chronic mucocutaneous candidiasis.[16]

CARD9 mutations related to CLR function, which plays a role in dectin-1 and dectin-2 signaling pathways, increase susceptibility to mucocutaneous and systemic candidiasis infections. Patients with CARD9 deficiency also show the absence of a complete Th17 cell response. Signal Transducer and Activator of Transcription (STAT)3 mutations are associated with major immunodeficiency syndrome in the form of hyper-IgE syndrome (HIES) resulting in severe IL-17 defects. Polymorphisms in TLR3 are associated with manifestations of *C. albicans* infection in chronic mucocutaneous candidiasis (CMC).[16]

Studies in HIV transgenic mice conducted by Goupil, *et al*, showed IL-17 defect and IL-22 dependent induction can increase susceptibility to oral candidiasis.[17] In untreated HIV patients there is an early impairment of Th17 function and depletion of specific CD4+ T cells against *C. albicans*. This is an important mechanism in the loss of immunity to mucosal candidiasis.[17,18] The detection of autoantibodies to Th17 cell cytokines such as IL-17A/F and IL-22 suggests candidiasis is an autoimmune disorder.[19]

Patients with systemic autoimmune diseases also have an increased risk of candidemia, although the risk is not as great as patients with HIV infection or congenital immunodeficiency. Vaquero-Herrero, *et al*, in 2020 found that of 1,040 patients with candidemia, 3.5% had systemic autoimmune diseases with rheumatoid arthritis being the most common type of autoimmune disease (27.8%). The most common *Candida* species found in systemic autoimmune patients was *C. albicans* (66.7%).[20]

CONCLUSION

Candida albicans, as a commensal organism, can turn into a pathogen influenced by *Candida* virulence factors, the host environment and the body's immune response. Innate immune responses that play a role include epithelial cells, stromal cells, PRR, nerve cells, neutrophils, monocytes, macrophages, NK cells, and dendritic cells. While, adaptive immunity against *Candida* is regulated by T-helper 1 and 17 cells that produce proinflammatory cytokines including IL-2, IL 17, IL 23, and IFN-γ. Adaptive immunity also has a role in activating the release of anti-*Candida* mediators from epithelial cells, such as defensins.

REFERENCES

1. Netea MG, Joosten LAB, van der Meer JWM, Kullberg BJ, van de Veerdonk FL. Immune defence against Candida fungal infections. Nat Rev Immunol. 2015;15(10):630–42. DOI: 10.1038/nri3897.
2. Anaissie EJ, McGinnis MR, Pfaller MA. Clinical mycology e-book. Elsevier Health Sciences; 2009.
3. Silva S, Negri M, Henriques M, Oliveira R, Williams DW, Azeredo J. Candida glabrata, Candida parapsilosis and Candida tropicalis: Biology, epidemiology, pathogenicity and antifungal resistance. FEMS Microbiol Rev. 2012;36(2):288–305. DOI: 10.1111/j.1574-6976.2011.00278.x.
4. Dismukes WE, Pappas PG, Sobel JD. Clinical mycology. Oxford University Press [Internet]. 2003. Available from: https://books.google.co.id/books?id=NNjnCwAAQBAJ.
5. Farrar J, Hotez PJ, Junghanss T, Kang G, Lalloo D, White NJ, et al. Manson's tropical diseases e-book. Elsevier Health Sciences; 2023.
6. Naglik JR. Candida immunity. In: Sulaiman MR, editor. New J Sci. 2014;2014:390241. DOI: 10.1155/2014/390241
7. Cheng SC, Joosten LAB, Kullberg BJ, Netea MG. Interplay between Candida albicans and the mammalian innate host defense. Infect Immun. 2012;80(4):1304–13. DOI: 10.1128/IAI.06146-11.
8. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med. 2015;373(15):1445–56. DOI: 10.1056/NEJMra1315399.
9. Lowman DW, Greene RR, Bearden DW, Kruppa MD, Pottier M, Monteiro MA, et al. Novel structural features in Candida albicans hyphal glucan provide a basis for differential innate immune recognition of hyphae versus yeast. J Biol Chem. 2014;289(6):3432–43. DOI: 10.1074/jbc.M113.529131.
10. Verma A, Gaffen SL, Swidergall M. Innate immunity to mucosal Candida infections. J Fungi (Basel). 2017;3(4):60. DOI: 10.3390/jof3040060.
11. Valeri M, Raffatellu M. Cytokines IL-17 and IL-22 in the host response to infection. Pathog Dis. 2016;74(9):111. DOI: 10.1093/femspd/ftw111.
12. Kashem SW, Kaplan DH. Skin immunity to Candida albicans. Trends Immunol. 2016;37(7):440–50. DOI: 10.1016/j.it.2016.04.007.
13. Conti HR, Gaffen SL. IL-17-mediated immunity to the opportunistic fungal pathogen Candida albicans. J Immunol. 2015;195(3):780–8. DOI: 10.4049/jimmunol.1500909.

14. Conti HR, Bruno VM, Childs EE, Daugherty S, Hunter JP, Mengesha BG, et al. IL-17 receptor signaling in oral epithelial cells is critical for protection against oropharyngeal candidiasis. Cell Host Microbe. 2016;20(5):606–17. DOI: 10.1016/j.chom.2016.10.001.
15. Richardson JP, Moyes DL. Adaptive immune responses to Candida albicans infection. Virulence 2015;6(4):327–37. DOI: 10.1080/21505594.2015.1004977.
16. Huppler AR, Bishu S, Gaffen SL. Mucocutaneous candidiasis: the IL-17 pathway and implications for targeted immunotherapy. Arthritis Res Ther. 2012;14(4):217. DOI: 10.1186/ar3893.
17. Liu F, Fan X, Auclair S, Ferguson M, Sun J, Soong L, et al. Sequential dysfunction and progressive depletion of Candida albicans-specific CD4 T cell response in HIV-1 infection. PLoS Pathog. 2016;12(6):e1005663. DOI: 10.1371/journal.ppat.1005663.
18. Auclair S, Liu F, Hu H. Loss of immune control in HIV-infected patients: How does mucosal candidiasis occur? Future Microbiol. 2017;12:5–8. DOI: 10.2217/fmb-2016-0194.
19. Glocker E, Grimbacher B. Chronic mucocutaneous candidiasis and congenital susceptibility to Candida. Curr Opin Allerg Clin Immunol. 2010;10(6):542–50. DOI: 10.1097/ACI.0b013e32833fd74f.
20. Vaquero-Herrero MP, Ragozzino S, Iriart X, Castano-Romero F, Sailler L, Sanchez-Gonzalez R, et al. Candida bloodstream infection in patients with systemic autoimmune diseases. Med Mal Infect. 2020;50(4):372–6. DOI: 10.1016/j.medmal.2020.01.014.