Candida and Toll-Like Receptors

Şayeste DEMİREZEN¹, Ayşegül YÜCEL¹, M. Sinan BEKSAÇ²

Ankara, Turkey

_Candida_ is a dimorphic fungus living as a commensal organism in human vagina. However it can cause infection under some conditions. Some factors, such as stratification of vaginal epithelial cells, natural flora and acidic pH, prevent infection by this organism. Recent studies identified that Toll-like receptor (TLR) proteins also play a role in protecting against infection. These receptors recognize _Candida_ cell wall components such as β-glucans, mannanproteins and chitin. When TLR’s interact with these biomolecules, TLR signaling pathway become active and various cytokines are produced. Morphogenesis from yeast form to pathogenic hyphal form is inhibited by these cytokines. In our review, we aim to clarify _Candida_, vulvovaginal candidiasis, TLRs and relationship between TLRs and _Candida_.

**Key Words:** Candida, Toll-like receptor, Infection


---

**Candida and Vulvovaginal Candidiasis**

_Candida_ is a yeast genus which is in _Blastomycetes_ class of _Deutoromycota_ phylum. This genus contains around 200 species.¹ Some species of _Candida_ lead to “vulvovaginal candidiasis” infection in the female genital tract. _C. albicans_, _C. glabrata_, _C. krusei_, _C. parapsilosis_, _C. kefyr_ ve _C. tropicalis_ are species being cause of vulvovaginal candidiasis (VVC) in women. As a result of studies, it is defined that _C. albicans_ is the most widespread cause of VVC worldwide. Furthermore, other species being responsible for VVC are more tolerant to antifungal therapy.²,³

Some symptoms may be seen in patients suffering from VVC. These symptoms are vaginal and vulvar pruritus, cottage-cheese vaginal discharge and burning.³,⁴ Broad spectrum antibiotic and high-estrogen containing contraceptive use, pregnancy, diabet mellitus, HIV and immunosuppression are risk factors for VVC.³,⁵

_C. albicans_ being the most common cause of VVC is a dimorphic and asexual fungus. It has four kinds of morphological forms under different conditions. These are blastospores, pseudohphae, true hyphae and chlamydospores.⁶ Blastospore form plays role in adherence to vaginal epithelial cells and asymptomatic colonization in vagina. Blastospores undergo morphogenesis to pathogenic hyphal form in response to various environmental conditions and symptoms appear.⁷,⁸ (Figure 1)

![Figure 1: Blastospore (left arrow) and hyphal (right arrow) forms of Candida](image)

_C. albicans_ has cell wall consisting of two layers; inner and outer membrane. Outer layer contains N-glycosylated or O-glycosylated mannanproteins and phospholipomannan glycolipid. Inner layer comprises polysaccharides such as β (1,6) - glucan, β (1,3) - glucan ve chitin.⁹,¹⁰ There are some differences between cell wall composition of blastospore and hyphal form. While cell wall of hyphal form has more chitin content, it has less β (1,6) – glucan and protein than blastospore form.¹¹,¹²

**Toll-like receptors**

The Toll gene was identified for the first time on _Drosophila_ in the early 1980’s.¹³ This gene codes Toll receptor which plays crucial role embryonic development and immunity of _Drosophila_ by signal transmission.¹⁴ As a result of genetic screening, structural homologues of Toll receptor are defined on mammals.¹⁵ These mammalian receptors are
named “Toll-like receptor” due to this homology. Thirteen kinds of TLRs are found in mammals. TLR1-10 is present in humans. They are related to pathogens and have a role in human immune system. 16

TLRs are type I transmembrane proteins. Their N-terminus are located outside of the cell, whereas their C-terminus are located on the side of cytoplasm. TLRs consist of three different domains. The part out of the cell is called as Extracellular Domain (ED). ED contains leucine-rich repeats (LRRs). This domain involves in recognizing many different ligands and therefore it acts as a receptor. The part in the cell membrane is called as transmembrane domain (TD) and the part in cytosol is called as Intracellular Domain (ID). TD consists of single transmembrane spanning and links the extracellular matrix to cytoplasm of cell. 13,17 Cytoplasmic parts of TLRs are responsible for signal transmission and have a small globular structure. It shares structural homology with cytoplasmic domains of interleukin-1 (IL-1) and interleukin-18 (IL-18) receptors. Thus, these domains of TLR proteins are known as "Toll – Interleukin-1 Receptor (TIR) domain".17 TIR domain pulls adapter proteins that are essential in signalling pathway.

TLRs are localized on macrophages, monocyte, dendritic cells and epithelial cell in different tracts. 16 These receptors are involved in recognizing ligands such as lipids, proteins and nucleic acids of pathogen organisms and creating immune response against them. When their ligands bind TLRs, conformational change occurs in the receptors. Signal is transmitted to cytoplasm and various transcription factors are activated. In this way, several cytokines taking part in immune response are produced.

Relationship between C. albicans and TLRs

C. albicans lives in vagina as a commensal organism and its blastospore form doesn’t lead to any infection. However, blastospore form is able to switch into hyphal form due to immunodeficiency or any other reason and it exhibits pathogenic feature. 7 Factors such as vaginal epithelial stratification, normal flora and acidic pH play important role in inhibition of this transformation. In recent studies, it is suggested that TLRs also involve in the prevention of this morphogenesis. 19

Several cell wall components and nucleic acids of C. albicans are ligands of TLR2, TLR4 and TLR9. β-glucans which are C.albicans cell wall component are recognized by “Dectin-1 receptor - TLR2 complex”. Phospholipomannan, another Candida cell wall biomolecule, is ligand of TLR2. Although the major ligands of TLR4 are bacterial lipopysaccharide (LPS), it is also responsible for recognizing O-linked mannosyl residues that are polysaccharide and compose mannoproteins of outer layer of Candida cell wall. 20 In addition, it is shown that DNA of C. albicans triggers immune response through TLR9. 21

Blastospore forms of Candida colonize on the vaginal epithelial cell. They adhere to vaginal epithelial cells slightly. TLRs on epithelial and dendritic cells recognize ligands in cell wall of blastospores and bind them. Thus, TLR signaling pathway is activated and IL-12 is produced. IL-12 induces T helper 1 (Th1) cells and this cells take part in secretion of interferon-γ (IFN-γ) and tumor necrosis factor alpha (TNF-α). Morphogenesis from blastospore into hyphae is kept under control by these protective cytokines. When the immune system fails to provide this protection because of broad-spectrum antibiotic use, chemotherapy etc., blastospores adhere to epithelial cells more stronger than normal state. Afterwards they switch to elongated hyphal form which can entire to deeper parts of the epithelium. Hyphal form is recognized by receptors on dendritic cells such as Complement receptor 3 and these cells phagocytose this form. Phagocytosis leads to inhibition of IL-12 and stimulation of T-helper 2 (Th2) cells. Hence, non-protective Th2 immune response occurs and some cytokines such as IL-4 and IL-10 are produced. In this way, whereas protective immunity is supressed in the presence of pathogenic hyphal form, non-protective immune response is activated. 19,22 (Figure 2)

In recent immunohistochemical studies, it was shown that immunohistochemical staining of TLR2 proteins in healthy oral and vaginal tissues was strong. However, its immunohistochemical staining was weak in candidosis and tissues on which high numbers of hyphal form of C. albicans were shown. 19,21 This findings suppose that blastospores are kept under control by TLR2 but its expression is suppressed in the presence of pathogenic hyphal form.

Conclusion

C.albicans is the most common cause of VVC. Its cell wall components are ligands of TLR2, TLR4 and TLR9 proteins.
When these ligands on blastosper cell wall bind TLRs, transformation into hyphal form is prevented by production of protective cytokines. If vaginal flora changes because of various reason, hyphal form can occur. Whereas protective immune response is suppressed, non-protective cytokines are produced against these form and Candidal infection is occurred.

References