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Candida and Toll-Like Receptors

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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, mannoproteins 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

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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)

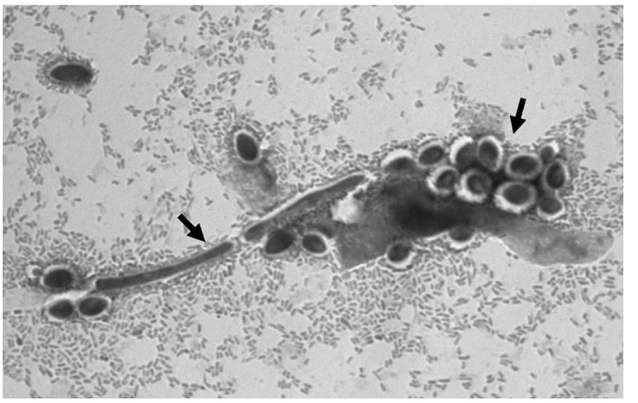

Figure 1: Blastospore (left arrow) and hyphal (right arrow) forms of Candida

C. albicans has cell wall consisting of two layers; inner and outer membrane. Outer layer contains N-glycosylated or O- glycosylated mannoproteins 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

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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.[18] 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 lipopolysaccharide (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 hepler 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, chemotheraphy 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, wheras protective immunity is supressed in the presence of pathogenic hyphal form, non-protective immune response is activated.[19,22] (Figure 2)

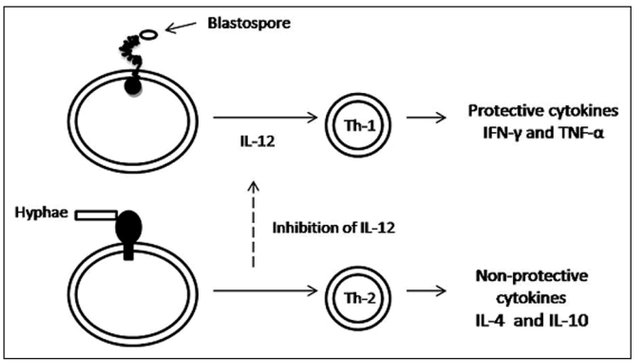

Figure 2: Blastospore form of Candida binds TLR's. This binding stimulates protective Th-1 immune response. Hyphal form is recognized by other receptors on dendritic cells and these cells phagocytose this form. Thus, whereas protective Th-1 immune response is inhibited, non-protective Th-2 immune response is stimulated.

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 candisosis and tissues on which high numbers of hyphal form of *C. albicans* were shown.[19,23] 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 blatospore 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.

Candida ve Toll - Benzeri Reseptörler

Candida, insan vajinasında kommensal olarak yaşayan ancak çeşitli durumlarda patojen özellik göstererek enfeksiyona neden olan dimorfik bir fungustur. Vajinal epitel hücrelerinin çok katlı olması, doğal flora elemanları, ortam pH'sının asiditesi gibi faktörler bu organizmanın enfeksiyon oluşturmasını önlemektedir. Son yıllarda yapılan çalışmalarda Toll-benzeri reseptör (Toll-like receptor = TLR) proteinlerinin de enfeksiyona karşı koruyucu rol oynadıkları belirlenmiştir. TLR'ler Candida'nın hücre duvarını oluşturan β-glukanlar, mannoproteinler ve kitin gibi çeşitli biyomolekülleri tanımaktadırlar. TLR'ler için ligand görevi yapan bu biyomoleküller reseptörlere bağlanarak TLR sinyal yolunun aktifleşmesine ve çeşitli sitokinlerin salgılanmasına neden olurlar. Bu sitokinler sayesinde Candida'nın blastospor formlarının patojen özellik gösteren hif forma dönüşmesi önlenmiş olur. Derlememizde de, Candida, vulvovajinal candidiasis, TLR'ler ve Candida - Toll-like reseptör ilişkisini anlatmayı amaçladık.

Anahtar Kelimeler: Candida, Toll-benzeri reseptör, Enfeksiyon

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