Review

Host Genetic Susceptibility in Recurrent Vulvovaginal Candidiasis: The TLR2/TLR4 Receptors

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Host Genetic Susceptibility in Recurrent Vulvovaginal Candidiasis: The TLR2/TLR4 Receptors

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Abstract

Vulvovaginal candidiasis (VVC) is a prevalent vaginal infection predominantly attributed to *Candida albicans*. A considerable proportion of women experience more than three episodes of VVC annually, a condition referred to as recurrent vulvovaginal candidiasis (RVVC). It is estimated that RVVC affects more than 130 million women globally each year and has a substantial negative impact on their quality of life, resulting in physical discomfort, psychological distress, and social stigma. Nevertheless, not all individuals who develop VVC progress to RVVC, suggesting that genetic variation may play a critical role in host susceptibility. The present review aims to evaluate the associations between genetic predispositions—specifically polymorphisms in Toll-like receptors 2 and 4 (TLR2, TLR4)—and RVVC. TLRs are essential for detecting pathogen-associated molecular patterns (PAMPs) and initiating immune responses. During RVVC episodes, Candida undergoes a reversible transition from the yeast form to the hyphal form, resulting in alterations in surface PAMPs, which are subsequently recognized by innate immune receptors expressed on vaginal epithelial cells. Polymorphisms in these receptors may modulate individual susceptibility to RVVC. This review examines the literature on the impact of specific polymorphisms in TLR2 and TLR4 on fungal recognition and infection. Furthermore, the interactions between TLRs and other elements of the innate immune system have also been explored. A deeper understanding of how genetic variability in immune receptors influences infection susceptibility could pave the way for personalized therapeutic strategies for RVVC, potentially involving immunomodulatory agents or antifungal treatments tailored to an individual's genetic profile.

Keywords: RVVC; vulvovaginal candidiasis; TLR2; TLR4; Toll like receptors; polymorphisms

1. Introduction

Vulvovaginal candidiasis (VVC) is a fungal infection of the vaginal tissue and the vulva of the female reproductive tract that is caused mainly by *Candida albicans*, an opportunistic fungal pathogen. Over 90% of VVC cases are attributed to *C. albicans*, whereas the remaining 10% are caused by nonalbicans Candida (NAC) species, such as Nakaseomyces glabratus (formerly *Candida glabrata*), Pichia kudriavzevii (formerly *C. krusei*), *C. tropicalis* and *C. parapsilosis* [1–3]. Recurrent vulvovaginal candidiasis (RVVC) is characterized by three or more symptomatic episodes of vulvovaginal candidiasis (VVC) within a year. RVVC is estimated to affect more than 130 million women in any given year, with a global annual prevalence of 3,871 per 100,000 females [4]. Although most women report experiencing RVVC for 1–2 years, some women endure recurrent infections for 4–5 years or even for decades. [5] This condition significantly impacts the quality of life of affected women, causing physical discomfort, psychological distress, and social stigma [6,7]. In qualitative research interviews, women with RVVC reported high levels of anxiety and fear regarding social interactions and dating as well as avoidance of sexual activity. [8]. RVVC also imposes a substantial economic

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burden [8]. In the United States, the total annual insurer and out-of-pocket costs for outpatient VVC treatment were estimated at US$368 million in 2017. Additionally, the estimated annual economic impact of RVVC in the United States in 2010 from lost work hours was US$1 billion. [4,9,10].

The pathogenesis of RVVC is multifactorial and involves environmental factors, genetic predispositions and immune responses, including the role of Toll-like receptors (TLRs) in the innate immune response [11,12].

2. Relevant Sections

2.1. Innate Immunity and Toll Like Receptors

Toll-like receptors, as evolutionarily conserved pattern recognition receptors, play a pivotal role in identifying pathogen-associated molecular patterns (PAMPs) [13,14], damage-associated molecular patterns (DAMPs) [15] and initiating immune responses. These transmembrane proteins trigger signaling cascades that lead to the production of proinflammatory cytokines, which are essential for orchestrating the body's defense against infections [15,16]. TLRs are classified into several types, each recognizing specific PAMPs. Thus, TLR2 recognizes bacterial lipopeptides from gram-positive bacteria, TLR4 detects lipopolysaccharides (LPS) from gram-negative bacteria, and TLR3 is activated by double-stranded RNA [17,18] from viruses. This specificity enables the innate immune system to tailor its response to various different pathogens effectively. The engagement of TLRs with their ligands triggers intracellular signaling pathways, primarily the MyD88-dependent and TRIF-dependent pathways, which culminate in the activation of transcription factors such as nuclear factor kappa B (NF-κB) and interferon regulatory factors (IRFs), leading to the expression of genes involved in inflammation and immune responses [18].

During vulvovaginal candidiasis infection, PAMPs on the Candida's surface are recognized by the innate immune system receptors, which activate intracellular signaling within vaginal epithelial cells [19]. These signals stimulate a proinflammatory cytokine response that recruits immune cells, such as phagocytes and T cells, to eradicate the fungus. [20].

2.2. Ligands of TLR2 and TLR4

TLR2 recognizes a wide range of ligands, which can be broadly categorized into microbial and endogenous components. Microbial ligands include triacylated and diacylated lipopeptides, peptidoglycans and lipoteichoic acid from bacteria as well as components from fungi and viruses [21]. Endogenous ligands, such as heat shock proteins (HSPs) and high mobility group box 1 (HMGB1), can also activate TLR2, contributing to sterile inflammation and tissue repair processes [22]. The interaction of TLR2 with these ligands triggers intracellular signaling cascades, primarily through the MyD88-dependent pathway, leading to the activation of NF-κB and the production of proinflammatory cytokines [23].

TLR4 is primarily activated by LPS, a major component of the outer membrane of gram-negative bacteria. The binding of LPS to TLR4 requires the presence of both the accessory protein CD14 and the MD-2 protein, which facilitates the formation of a signaling complex [24]. This interaction initiates a robust immune response characterized by the production of proinflammatory cytokines, chemokines, and the recruitment of immune cells to the site of infection. In addition to LPS, TLR4 can recognize a variety of other ligands, including endogenous molecules such as HSPs, fibronectin, and hyaluronic acid, which can be released during tissue injury or inflammation [25]. These interactions have also been implicated in chronic inflammatory responses in various diseases, including cancer and autoimmune disorders [26].

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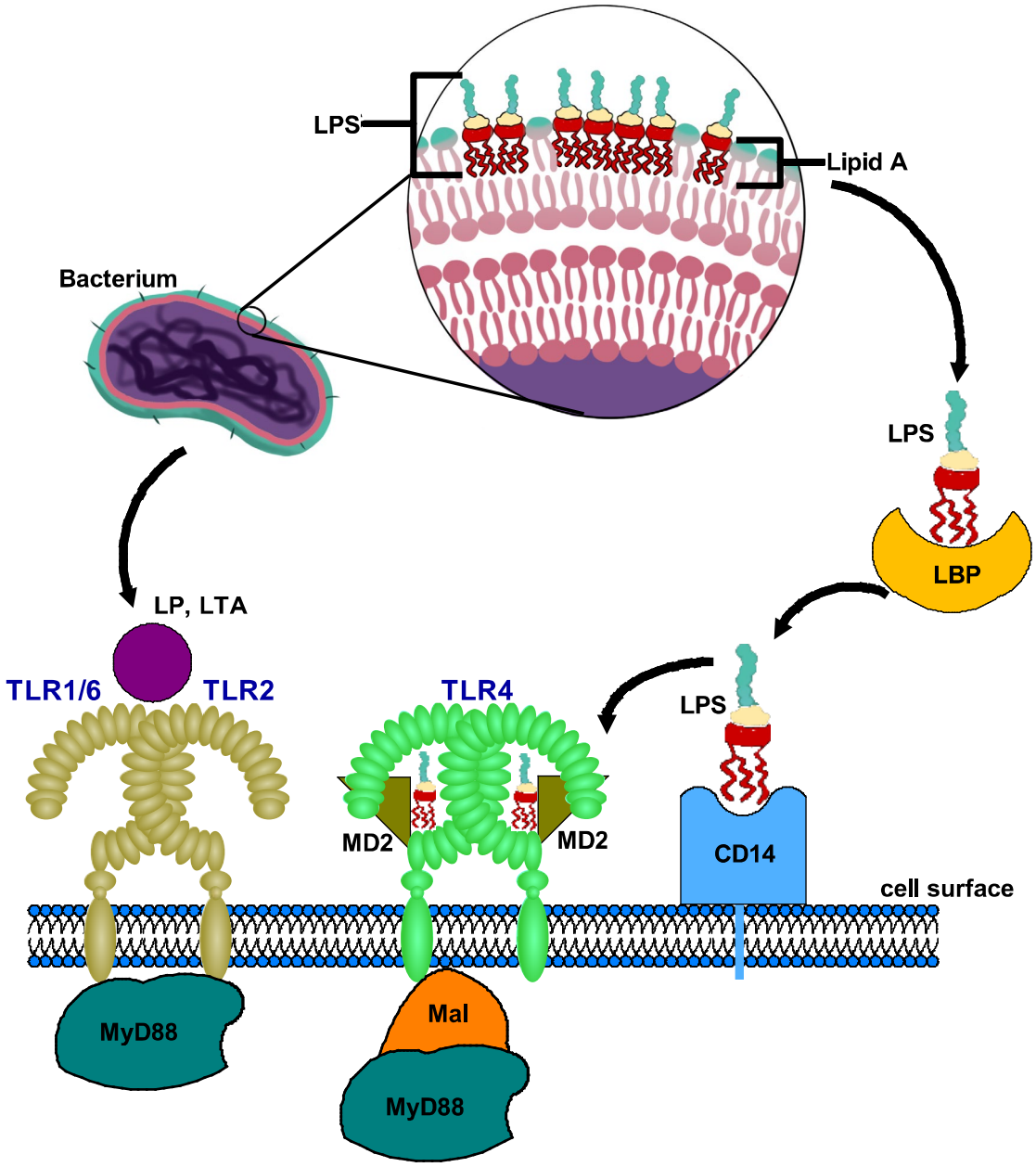

Figure 1. Ligand recognition by TLR4 and TLR2 receptors. A. Recognition of LPS by TLR4: LPS, released from the outer membrane of gram-negative bacteria. LBP binds to LPS and presents it to CD14, which eventually leads to formation of TLR4-MD-2-LPS complex, resulting in dimerization of TLR4 subunits triggering TLR4 pathway. MD2 is necessary for TLR4 to bind to LPS and homodimerize. B. Recognition of LP, LTA by TLR2: TLR2 forms a heterodimer on the cell surface with co-receptors TLR1 or TLR6. The TLR2/TLR1 and TLR2/TLR6 heterodimers specifically bind LP, LTA released from gram-positive bacteria. The ligand binding to heterodimer brings the intracellular TIR domains close to each other and initiate signaling. Abbreviations: LPS, lipopolysaccharide; LBP, LPS binding protein; LTA, lipoteichoic acid; LP, lipopeptide; MD2, myeloid differentiation factor 2; Mal, MyD88-adapter-like; MyD88, myeloid differentiation 88 protein.

2.3. Signaling Pathways of TLR2 and TLR4

Upon ligand binding, TLR2 primarily activates the MyD88-dependent signaling pathway, which leads to the recruitment of various signaling molecules, including interleukin-1 receptor-associated kinase (IRAK) and tumor necrosis factor receptor-associated factor 6 (TRAF6) [23,27]. This cascade results in the activation of NF-κB and mitogen-activated protein kinases (MAPKs), which are crucial for the transcription of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 [28]. Additionally, TLR2 can also activate the TRIF-dependent pathway, although this occurs less frequently. This

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pathway is associated with the production of type I interferons and is particularly important in the context of viral infections [29]. The ability of TLR2 to engage multiple signaling pathways underscores its versatility in modulating immune responses.

TLR4 signaling also occurs through two pathways: the MyD88-dependent pathway and the TRIF-dependent pathway. The MyD88-dependent pathway is activated upon LPS binding and leads to the recruitment of IRAK and TRAF6, resulting in NF-κB activation and proinflammatory cytokine production [30]. This pathway is critical for the early immune response to bacterial infections. The TRIF-dependent pathway is also activated by the binding of LPS to TLR4 and involves the recruitment of TRIF, leading to the activation of interferon regulatory factors (IRFs) and the subsequent production of type I interferons [31]. This pathway is particularly important for antiviral responses and the regulation of adaptive immunity. The dual signaling capabilities of TLR4 allow for a robust and multifaceted immune response to a variety of pathogens.

Recent studies have highlighted the crosstalk between the TLR2 and TLR4 signaling pathways, suggesting that simultaneous activation of both receptors can enhance the immune response. For example, the costimulation of TLR2 and TLR4 in macrophages synergistically increases the production of proinflammatory cytokines, amplifying the overall immune response to infections [32]. This crosstalk may also contribute to the development of chronic inflammatory conditions, where persistent activation of TLRs can lead to tissue damage and disease progression [33].

2.4. Role of TLR2 and TLR4 in Fungal Recognition and RVVC

TLRs are integral to the ability of the innate immune system to detect fungal infections. Specifically, TLR2 and TLR4 have been shown to recognize components of the Candida cell wall, such as β-glucans and mannan, leading to the activation of inflammatory pathways and cytokine production [6,34]. This recognition is vital for the recruitment of immune cells to the site of infection, facilitating phagocytosis and the subsequent clearance of the pathogen [35].

TLR2 recognizes phospholipomannans [36], which leads to the local production of proinflammatory cytokines such as IL-1β and IL-6, which are key mediators of immune cell recruitment to the site of infection [11,37]. Similarly, TLR4 responds to O-linked mannans [38], contributing to the inflammatory response. Genetic polymorphisms in these receptors can influence an individual's susceptibility to RVVC [12]

Research indicates that TLR signaling not only promotes protective immune responses but also contributes to inflammatory pathology, potentially exacerbating the symptoms of RVVC [34,39]. This dual role underscores the complexity of TLR-mediated responses in fungal infections, where an excessive immune response may result in tissue damage and persistent symptoms.

The activation of TLRs leads to the production of various cytokines that orchestrate the immune response against Candida infections. In patients with RVVC, an exaggerated cytokine response, particularly in the presence of hyphae, has been observed, which are formed almost exclusively by *Candida albicans* [6,40]. This heightened inflammatory response is believed to contribute to the symptoms associated with RVVC, negatively impacting quality of life.

Cytokines such as IL-1β and TNF-α are crucial for recruiting neutrophils and macrophages to the site of infection, promoting phagocytosis and fungal clearance [41]. However, excessive cytokine production can lead to chronic inflammation, perpetuating the reinfection-inflammation cycle, which is characteristic of RVVC [42,43]. Understanding the balance between protective and pathological immune responses is essential for the development of targeted therapies for RVVC.

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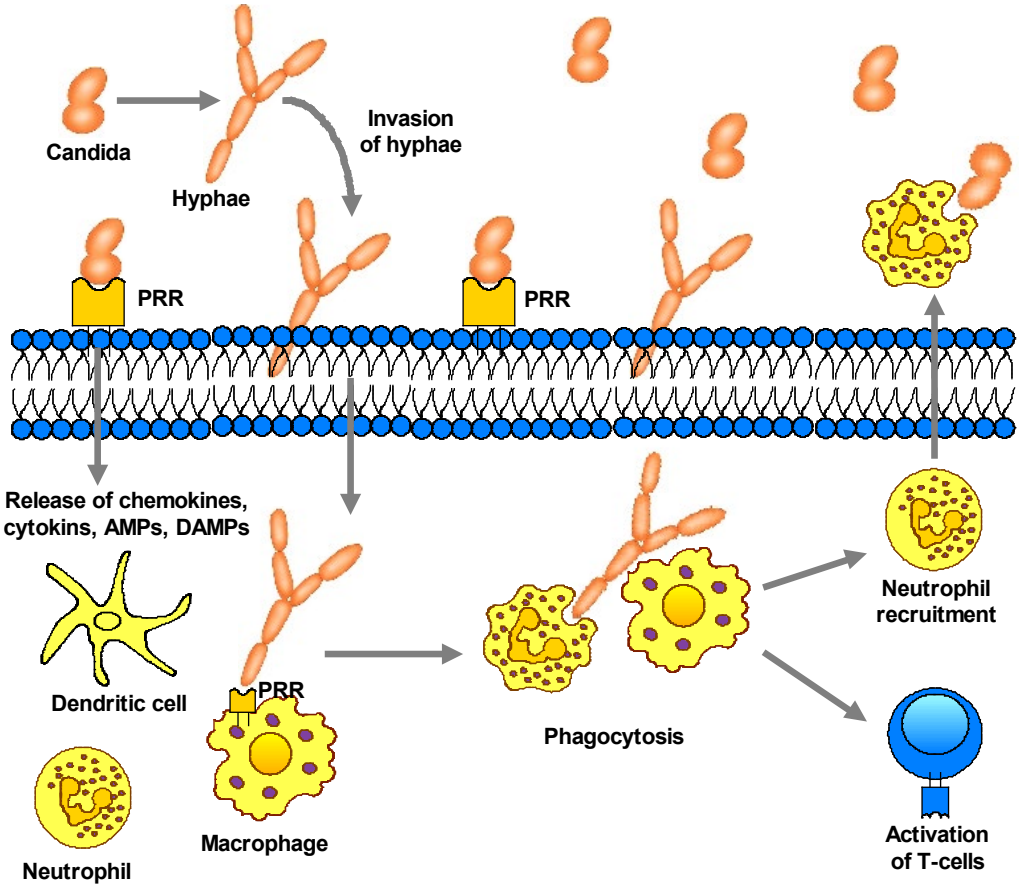

Figure 2. During the infection process, Candida undergoes reversible yeast-to-hyphae transition, which causes changes in the type of surface carbohydrates, affecting the adhesion and invasion of vaginal epithelial cells. Candida infects vaginal vaginal epithelial cells directly through the invasion of hyphae and activates PAMPs with pattern recognition receptors (PRRs). In response to this, contact inflammatory immune mediators—chemokines, cytokines, antimicrobial peptides or damage-associated molecular patterns—are secreted, subsequently recruiting innate immune cells, such as macrophages, dendritic cells and neutrophils. These cells also recognize PAMPs through PRRs on their surfaces, bind to the pathogen, and stimulate its removal by phagocytosis.

3. Discussion

3.1. Genetic Polymorphisms and Immune Response

Single nucleotide polymorphisms (SNPs) strongly influence innate immune responses to pathogenic challenges and disease outcomes; therefore, individual susceptibility to infections varies, with some people being predisposed to certain infections and others being more resistant [44]. In this context, host genetic variants in PRRs have long been thought to impair the antifungal immune response in RVVC patients. Genetic variations, including polymorphisms in TLRs and mannose-binding lectin, which may increase susceptibility to VVC [20], have been observed in women with RVVC [4,45]. Single-nucleotide polymorphisms and other genetic alterations affecting key signaling proteins in the host may prompt the onset of VVC and increase susceptibility to RVVC [20,46]. Genetic variants in pattern recognition receptors or signal transducers have been found to impair the antifungal immune response in patients with RVVC [20]. Variants in TLR2 and TLR4 have been associated with altered immune responses to Candida infections, suggesting that genetic predisposition plays a role in the pathogenesis of RVVC [47,48]. For example, certain TLR polymorphisms may impair the recognition of Candida components, leading to inadequate immune responses and increased susceptibility to recurrent infections [12].

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3.2. Polymorphisms in TLR4

The TLR4 gene is known to harbor several SNPs, with the most studied being Asp299Gly (rs4986790) and Thr399Ile (rs4986791). These two polymorphisms are in linkage disequilibrium. Linkage disequilibrium refers to the nonrandom association of alleles at different loci, which can often be observed in genetic studies. Several studies have reported that the Asp299Gly and Thr399Ile polymorphisms frequently cosegregate. Senhaji et al. conducted a meta-analysis that confirmed the presence of linkage disequilibrium between these two TLR4 polymorphisms, noting that they are often coinherited together as a haplotype [49]. This finding is supported by the work of Ferwerda et al., who discussed how the proinflammatory phenotype associated with the Asp299Gly allele may have evolutionary implications, further suggesting the coinheritance of these alleles [50]. The TLR4 Asp299Gly Thr399Ile haplotype has been reported to alter the leucine-rich repeat region of the receptor and decrease the efficiency of ligand recognition [51].

Numerous studies have revealed a connection between TLR4 polymorphisms and susceptibility to infections. For example, the Asp299Gly polymorphism has been linked to a hypo-responsive state to LPS [51], resulting in increased susceptibility to infections caused by gram-negative bacteria [52,53]. This hyporesponsiveness is particularly evident in individuals with the Asp299Gly variant, who exhibit diminished production of proinflammatory cytokines upon LPS stimulation [52,54]. Individuals carrying the Asp299Gly variant are at increased risk of developing severe infections, such as those caused by *Haemophilus influenzae* and *Mycobacterium tuberculosis* [53]. A recent meta-analysis revealed that the TLR4 polymorphic locus rs10759932, which is located in an upstream regulatory region of the TLR4 gene, increased the risk of pulmonary tuberculosis [55]. The G allele of rs4986790 (Asp299Gly mutation) is also an independent risk factor for pulmonary tuberculosis [55].

Two other studies have demonstrated a link between this SNP and an increased risk of septic shock due to infection by gram-negativenegative individuals [56,57]. The TLR4 Asp299Gly haplotype has also been associated with an increased incidence of systemic inflammatory response syndrome [58]. Ziakas et al. conducted a meta-analysis that highlighted the association of the TLR4 896 A>G and 1196 C>T SNPs with an increased risk for various infections, including malaria and other parasitic diseases [59]. Both the TLR4-Asp299Gly and the TLR4-Thr399Ile variants confer an increased risk of severe malaria in Ghanaian children, linking these SNPs to disease manifestation [60]. Rasouli et al. further elucidated the role of TLR4 polymorphisms in visceral leishmaniasis, demonstrating a higher prevalence of certain SNPs among affected individuals [61].

The strongest association between TLR4 polymorphisms and disease susceptibility has been detected in respiratory syncytial virus (RSV) infection, where infants heterozygous for Asp299Gly and Thr399Ile showed increased susceptibility to infection [62]. Silva et al. reinforced this notion through a comprehensive meta-analysis, indicating that the TLR4 896A/G polymorphism is linked to a diverse spectrum of infections, emphasizing its complex role in immune response modulation [63].

The mechanisms by which TLR4 SNPs influence disease susceptibility are multifaceted. The Asp299Gly polymorphism has been shown to alter TLR4 signaling pathways, leading to decreased NF-κB activation and altered cytokine production [64]. This alteration can result in a diminished inflammatory response, which may predispose individuals to infections. Hold et al. demonstrated that both the Asp299Gly and Thr399Ile SNPs can upregulate the expression of TRIF-dependent genes, which play a catalytic role in the immune response to pathogens [54]. These findings suggest that while these polymorphisms may confer susceptibility to certain infections, they may also enhance responses to others, thus demonstrating the intricate balance of immune regulation.

3.2. TLR4 Polymorphisms and Fungal Infections

TLR4 variants also influence antifungal immune responses. The TLR4 Asp299Gly Thr399Ile haplotype is associated with the development of invasive pulmonary aspergillosis (IPA) in donors of allogeneic stem cell transplantation (HSCT) [65]. However, the exact mechanism remains unknown, particularly since no fungal ligands have been identified to date. One proposed mechanism is that

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variations in the TLR4 gene alter cytokine production, which may affect the inflammatory response and the clearance of fungal infections [12].

The crystal structure of TLR4 Asp299Gly/Thr399Ile has been solved as a complex with MD-2 and LPS [66,67]. Compared with the wild-type TLR4/MD-2/LPS complex structure, the overall arrangements of the two complexes were similar, and topical differences were present around only the Asp299Gly SNP site, which induced a structural change that modulated the surface properties of TLR4. This effect may be more apparent upon stimulation of TLR4 with ligands with weak agonistic activity. The impact of the Thr399Ile change was minor, as nearly no structural differences were observed [67].

3.3. Polymorphisms in TLR2

TLR2, as a heterodimer with TLR1 or TLR6, recognizes a large number of common bacterial motifs, including lipopeptides, peptidoglycans, glycosylphosphatidylinositol-linked proteins and zymosan. Dysregulation of TLR2 signaling due to genetic polymorphisms can lead to altered immune responses, potentially increasing susceptibility to infectious diseases [68].

Several single nucleotide polymorphisms (SNPs) have been identified in the TLR2 gene, with the most studied being Arg677Trp (rs121917864) and Arg753Gln (rs5743708). These polymorphisms can affect the receptor's ability to recognize PAMPs and modulate immune responses [68]. For example, the Arg677Trp variant has been associated with altered cytokine production in response to bacterial infections, suggesting a potential link to increased susceptibility to infectious diseases [69]. Arg677Trp is common in African and Asian populations but is almost absent among Caucasian populations [44]. In vitro, this SNP has been shown to inhibit both *Mycobacterium leprae*- and *Mycobacterium tuberculosis*-mediated NF-κB activation and production [70]. In a studied Korean population and a Tunisian population, this SNP was associated with leprosy [71] and susceptibility to tuberculosis [72], respectively. Moreover, a study conducted in Iran revealed that the TLR2 Arg677Trp polymorphism was associated with a greater likelihood of infection among individuals exposed to *Mycobacterium tuberculosis* [73]. A meta-analysis revealed that the TLR2 Arg677Trp polymorphism was associated with an increased risk of severe periodontitis, confirming its role in modulating the immune response to oral pathogens [74].

Studies have also revealed that the TLR2 Arg753Gln polymorphism is associated with increased susceptibility to tuberculosis and other infections. In this context, Bhanothu et al. reported that the TLR2 Arg753Gln variant is associated with the susceptibility of females to tuberculosis, suggesting that this SNP may influence immune responses to mycobacterial infections [75,76]. This polymorphism was also associated with an increased risk of developing tuberculosis in a Turkish population [77], along with a significantly increased risk for some individuals to develop infective endocarditis [78]. Additionally, TLR2 polymorphisms have been studied in the context of viral infections. Research has shown that certain TLR2 variants may influence the immune response to viruses such as dengue and HIV, potentially affecting disease outcomes [79]. Kang et al. demonstrated that homozygosity for the TLR2 Arg753Gln SNP is a risk factor for cytomegalovirus disease following liver transplantation, indicating its potential role in modulating immune responses in transplant patients [80]. Another study indicated that TLR2 polymorphisms are associated with the severity of dengue virus infection, suggesting that genetic variations in TLR2 may impact the host's ability to control viral replication [81].

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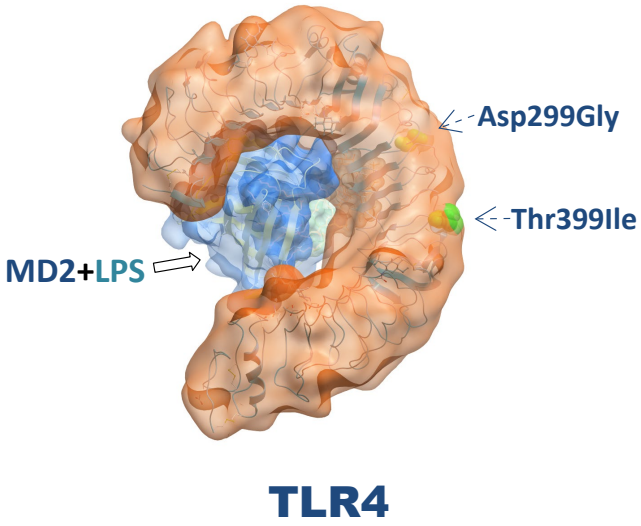

Figure 3. Three dimensional structure of TLR4 and localization of their major polymorphisms.

3.4. TLR2 Polymorphisms and Fungal Infections

The role of TLR2 in fungal infections has also been explored, particularly in the context of invasive fungal diseases. Studies have brought to light that TLR2 is involved in the recognition of fungal components, such as β-glucans, and plays a critical role in the immune response to fungi such as *Candida albicans* and Aspergillus species [82]. Polymorphisms in the TLR2 gene may affect susceptibility to these infections, with certain variants associated with an increased risk of invasive fungal disease in immunocompromised patients [83]. For example, the R753Q TLR2 polymorphism increased the risk for candidaemia in a limited study through decreased IFN-γ and IL-8 levels [84]. Similarly, a study examining TLR2 polymorphisms in hematopoietic stem cell transplant recipients revealed that specific genetic variants were linked to an increased risk of developing invasive aspergillosis, underscoring the importance of TLR2 in antifungal immunity [85].

The Pro631His (rs5743704) SNP in TLR2 has been implicated in the development of idiopathic recurrent vulvovaginal candidiasis (RVVC). More specifically, the TLR2 Pro631His polymorphism was associated with an almost 3-fold increase in susceptibility to RVVC. [86]. Moreover, TLR2 deficiency influences susceptibility to systemic candidiasis in mice [87].

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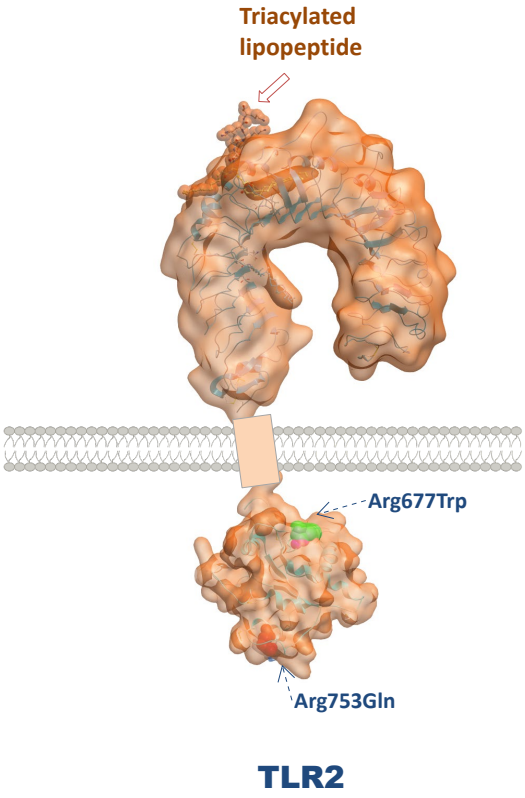

Figure 4. Three dimensional structure of TLR2 and localization of their major polymorphisms.

3.5. Polymorphisms in TLRs, Other Than TLR2 and TLR4, and Fungal Infections

Genetic variations in the TLR1, TLR3, TLR5 and TLR9 TLRs have also been proposed as risk factors for fungal disease. TLR1 appears to be an important repository of genetic variability, increasing susceptibility to candidaemia [88]. For TLR9, the variant rs5743836 (in the promoter region) is associated with the development of allergic bronchopulmonary aspergillosis (ABPA) [89]. Another association involves TLR5, in which an SNP leading to an early stop codon (Arg392X) has been shown to disrupt flagellin recognition [90]. In HSCT recipients, the presence of this variant was associated with the development of IPA [90], suggesting a likely important antifungal function of TLR5. Despite being classically acknowledged as a prototypical receptor for double-stranded RNA, TLR3 has been implicated in fungal recognition and activation of adaptive immune responses. In particular, the regulatory variant rs3775296 in TLR3 was demonstrated to increase the risk of IPA after HSCT [91]. However, the nonsynonymous SNP rs3775291 (Leu412Phe) in TLR3 was detected more frequently in patients suffering from chronic mucocutaneous candidiasis (CMC) [92]

3.6. Interactions with Other Immune Components

The immune response to Candida spp. is not solely dependent on TLRs; other components of the innate immune system, such as C-type lectin receptors (CLRs), also play a significant role. CLRs, including Dectin-1, work in concert with TLRs to enhance the recognition and clearance of Candida [42,93]. The collaboration between TLRs and CLRs is vital for a comprehensive immune response, as they recognize different fungal components and activate distinct signaling pathways. In this context, genetic factors, such as those related to the mannose-binding lectin (MBL) pathway, increase the risk of RVVC. MBL deficiency has been shown to increase susceptibility to RVVC, highlighting the importance of a well-coordinated immune response in preventing recurrent infections [94]. The interplay between these genetic factors and the immune system underscores the need for a comprehensive understanding of the immunological landscape in RVVC patients.

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Moreover, the interaction between TLRs and other PRRs, such as Dectin-1, is crucial for a robust antifungal response. Dectin-1 recognizes β-glucans, while TLRs detect other fungal components, creating a synergistic effect that enhances the immune response against Candida [42,95]. This interplay underscores the importance of a well-functioning innate immune system in preventing RVVC.

Furthermore, the role of the inflammasome in the immune response to Candida spp. has gained attention. The NLRP3 inflammasome, for example, is activated in response to Candida spp. infection, leading to the processing of proinflammatory cytokines [41]. This interaction highlights the complexity of the immune response, where multiple pathways converge to combat fungal infections.

4. Conclusions, Clinical Implications and Future Research Directions

The identification of specific TLR polymorphisms associated with RVVC risk can aid in the development of targeted treatments and prevention strategies. Understanding how genetic variability in immune receptors affects infection susceptibility opens possibilities for personalized therapeutic approaches, potentially using immunomodulators or antifungal therapies tailored to individual genetic profiles. TLRs themselves are also potential targets for therapeutic interventions. TLRs can be both friends and foes since improperly regulated TLR signaling can result either in the overactivation of immune responses, leading to pathologic inflammation, or in diminished inflammatory responses, which may predispose individuals to infections. In this context, recent efforts have focused on the development of both TLR antagonists as anti-inflammatory drug candidates and TLR agonists as immunotherapeutics [76,96]. Further research is warranted to investigate other polymorphisms in TLR-related pathways and their potential interactions with environmental factors that may contribute to RVVC, as well as to elucidate how these pathways might be therapeutically targeted to prevent recurrence.

This literature review summarizes current insights into the genetic underpinnings of RVVC, focusing on polymorphisms in TLR2 and TLR4 as significant factors in the host immune response, and highlights future directions for research and clinical practice to improve outcomes for those affected by RVVC.

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