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The dual role of Toll-like receptor10

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Abstract

Toll-like receptors (TLRs) are a class of pattern recognition receptors (PRRs) family that identify pathogen-associated molecular patterns (PAMPs) derived from microbes and activate immune cell responses. Following ligation of TLRs, different adaptor and transcription molecules such as myeloid differentiation primary response gene 88 (MyD88) and nuclear factor kappa B (NF-kB) are involved and trigger pro-inflammatory responses. The human Toll-like receptor 10 (hTLR10) is a novel member of the Pattern recognition receptors (PRRs) family. Its unique cytoplasmic domains lead to induction of both inflammatory and anti-inflammatory properties and thus regulates the function of immune responses . Recent studies have reported the association of TLR10 polymorphisms with many inflammatory diseases and human cancers. Despite the proven role of TLR10 in the induction of proinflammatory cytokines and chemokines, other studies have proven an anti-inflammatory role of TLR10. Accordingly, TLR10 suppresses proinflammatory cytokine production via negative regulation of MyD88 and the Akt (protein kinase B) and MAPK (mitogen-activated protein kinase) signaling pathways. This review aimed to provide answers for these conflicting findings (Inflammatory and anti-inflammatory properties of TLR10) to further identify distinct biological functions of TLR10.

Keywords: Toll-Like Receptor, Innate Immunity, Inflammation, Anti-inflammation

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- **Introduction**

Overview of TLR10

TLRs are highly conserved transmembrane proteins that are involved in innate immune responses through the recognition of variety of endogenous and exogenous stimuli (1, 2). They are mainly expressed on cells which act as antigen-presenting cells such as dendritic cells, and their signaling activity translates innate immunity to adaptive immunity (3).

To date, 13 members of TLRs have been identified including TLR1–TLR10 in humans (4) and TLR1–TLR9, TLR11–TLR13 in mice (5). A novel toll-like receptor (TLR) was reported by Tsung-Hsien Chuang and Richard J.Ulevitch in 2001 and termed human TLR10 (6). Many studies reported that TLR10 is expressed in humans but not in mice (7-9). Althogh functional mouse homologue of hTLR10 has not yet been identified, it is reported the low level expression of TLR10 in Plasmacytoid dendritic cells (PDCs) from rat spleen (10, 11). Also, TLR10 protein is expressed by a retroviral sequence in mouse TLR10 gene (12). On the other hand, presence of hTLR10 (CD290) in human DNA genomes has been proven using the expressed sequence tag (EST) database of NCBI with a blast program (13). Protein analysis has shown that the structure of TLR4 is similar to other TLRs (14). The evolutionary relationship of 3 of the 10 members of the hTLRs suggested that they were more closely related to hTLR1 and hTLR6 compared to other TLRs (6, 15).

Many efforts have been made to identify the properties of TLR10, like its ligand and signaling pathway function. Some pathogen-associated molecular patterns (PAMPs) such as Listeria Monocytogenes and Salmonella Typhi murium (16), influenza viral (ribonucleoprotein RNP) (17), helicobacter pilory (18), and double strand RNA (dsRNA) (19) are introduced as a ligand forTLR10. TLR 10 remains the only orphan member among the human TLRs that is able to homodimerize or heterodimerize with TLR1 and TLR2 (20). Similar to other members of TLR family, hTLR10 contained the repeated leucine-rich (LRRs) domains, an extracellular cysteine-rich domain, and a transmembrane with a TIR domain (21). The crystal structure of the homodimer of hTLR10 revealed cytoplasmic toll/IL-1 receptor (TIR) domain (22). The overall structure of TIR domains is largely the same between TLR members (23). However, TIR domain orientation of TLR2/TLR1 heterodimer is very different from hTLR10 homodimer in which interactions occur between the BB-loop of TLR1 and DD-loop of TLR2 (24). Different interactions mainly occur between hydrophobic residues in the BB-loops and the αC-helices (25). Due to the exposure to the surrounding solvent, the BB-lope of TIR domain may be important to recruit adaptor protein (26). The evolutionary analysis of proteins has revealed that TLR10 has a more similar structure to hTLR1 and hTLR6 than other TLR molecules (27).

- **Distribution Of TLR10**

The human TLR10 has been detected in plasmacytoid dendritic cells from peripheral blood B cells, B cell lines, and Dendritic Cells (DCs) subset derived from CD34+ progenitor cells (10, 28, 29). TLR10 is mainly restricted to B cells and has a role in B cell development and maturation

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(30). Unlike naïve B cells, memory B cells express constitutively high levels of TLR10 along with low levels of TLR2, TLR4, and TLR 8 (28). High level of expression of TLR10 is detected in immune tissues such as lymph node, lung, and spleen, where immune cells are abundant (31). Similar to peripheral blood B cells, the marginal zone B lymphocyte in normal spleen expresses a significant amount of TLR10 (32). While human TLR10 is not expressed in tonsillar plasma cells and hematopoietic stem cells (33, 34). Moreover, TLR10 is expressed on airway smooth muscle cells (ASMCs), trophoblast, and human placental tissue (6). Expression of TLR10 in smooth muscles in lungs and vascular endothelium of both inflamed and control animals (chickens, cattles, pigs, rats, and dogs) has been established in a research conducted by Balachandran Y et al. (35).

- **Function and Ligand**

Human TLR10 is a largely functional receptor on surface B cells and pDCs which activates intracellular signaling pathway via MyD88 (10, 36, 37). No specific ligand has been identified for TLR10 (10). However, TLR10 in cooperation with TLR2 can identify triacylated lipopeptide agonists (38). Typical TLR-associated signaling pathway such as activation of NF-κB, production of Interferon beta (IFN-β), or Interleukin 8 (IL-8) could not be induced by hTLR10 (39). Resting B cells stimulation with Staphylococcus aureus, anti-CD40, and anti-Human IgM (μ-chain specific) results in mRNA expression of both TLR9 and TLR10 [8]. In addition, cytosine-phosphate-guanine (CpG) DNA pattern can increase expression of TLR10 through potential positive regulation [48]. Moreover, the synthesized Plasmodium falciparum erythrocyte membrane protein 1- cysteine rich interdomain 1α (PfEMP1–CIDR1α) in a dose depended and lipopeptides could activate TLR10 similar to other members of the TLRs family, contained TIR domins [8, 49, 50].

It is reported that stimulation of TLR10 by Salmonella typhimurium and Listeria monocytogenes, not heat killed bacteria, leads to the production of large amounts of IL8 [13].On the other hand, many studies have reported that involvement of TLR10 is not restricted to bacterial infection and it may sense component of influenza virus A, viral ribonucleoprotein (RNP), and double-stranded RNA (dsRNA), which triggers an innate immune response [15, 51, 52]. TLR10 recognizes human immunodeficiency virus-1 (HIV-1) proteins as a PAMP which resulting in IL-8 secretion via activation of NF-kB (40). It is reported by Jiang et al. that activation of TLR10 resulted in suppression of both myeloid differentiation primary response gene 88/TIR domain–containing adaptor inducing IFN-β (MyD88/TRIF)-dependent and independent signaling pathway in mononuclear cell, which inhibits production of inflammatory mediators, including IFN-β and interleukin 6 (37). B cell proliferation induced by S.aureus Cowan strain, a B cell mitogen, could be suppressed by TLR10 engagement (41). Also, the signal transduction, B cell proliferation, and cytokine production could be suppressed by anitybody mediated- TLR10 ligation on primary human B cells (42). Anti-TLR10 antibodies can affect more than 30 genes such as activation induced cytosine deaminase (AICDA), chemokine ligand 3 (CCL3), and CCL4, involved in B cell signaling, migration, and immune function (18). However,

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Hess NJ et al. have observed B cell development and antibody production in hTLR10 transgenic mice was not significant (43).

- **Proinflammatory and Anti-inflammatory Properties of TLR10**

All TLRs mediate their function via MyD88 and interleukin-1 receptor-associated kinase 4 (IRAK-4), except TLR3, which requires the signaling TRIF adaptor (44). The TLR2 and TLR4 heterodimers with TLR1, TLR6, and TLR10 invoke the TIR Domain Containing Adaptor Protein (TIRAP) adaptor (Figure 1), whereas TLR3, TLR7, TLR8, and TLR9 need UNC-93B (ubiquitinated-protein 93B) for proper intracellular localization (2). The signaling activity of TLR10 requires the downstream adapter molecule MyD88 which is usually engaged by other TLRs (6). The TLR10 antibody is able to suppress the phosphorylation of the mitogen-activated protein kinase (MAPK), JNK (c-Jun N-terminal kinases), but not P38 or extracellular signal-regulated kinases (ERKs) (6). Moreover, the anti-TLR10 antibodies are able to suppress Akt (Protein kinase B, PKB) signaling when stimulated with anti-B cell receptor antibody (αBCR), suggesting TLR10 may also be able to target the Phosphorus triiodide (PI3) kinase pathway (4). Increased expression of TLR7 and TLR10 was detected in B cells after stimulation by CIDR1α (cysteine-rich interdomain region 1α) and PfEMP1 from plasmodium falciparum. Furthermore, PfEMP1–CIDR1α recruits MYD88 and activates the downstream kinases such as IKBα ERK1/2 and p38 in human B cells (45). In a study conducted by Khoo JJ et al. the chimera receptor CD4-TLR10 can initiate the downstream signaling via NF-κB (46) which in turn leads to production of Tumor necrosis factor alpha (TNF-α) in macrophages (17). It has shownthat NF-AT (nuclear factor of activated T cells) and forkhead box P3 (FOXP3) transcription factors regulate the expression of TLR10 in Tregs cells (47) and attenuates pro-inflammatory responses. Following the overexpression of TLR10 and TLR2 on the surface of HEK293 cells (a cell line derived from human embryonic kidney cells) initiates NF-κB activation, TNF-α, and IL-8 production upon ligation of TLR10 by helicobacter pylori (H. pylori) lipopolysaccharide (LPS) (18). Tim Regan et al. have reported that TLR10 knockdown reduced IL-8, CCL20 (C-C Motif Chemokine Ligand 20), and CCL1 in the THP-1 macrophage cell line. They also observed NF-κB activation in L. monocytogenes infected epithelial cells following ligation of TLR2 and TLR10 (48). In the rheumatoid arthritis (RA) patients, the IL-1β serum concentrations is significantly correlated with TLR10 expression on the CD19+CD27+ B cell subset, which is positively increased with disease activity (39, 49). Oxidative stress (H2O2) in patients with type-2 diabetes and obesity induces the TLR10 downstream pathways through MAPK/NF-κB signaling and increases the production of proinflammatory cytokines/chemokine IL-23A and CCL-5 (50).

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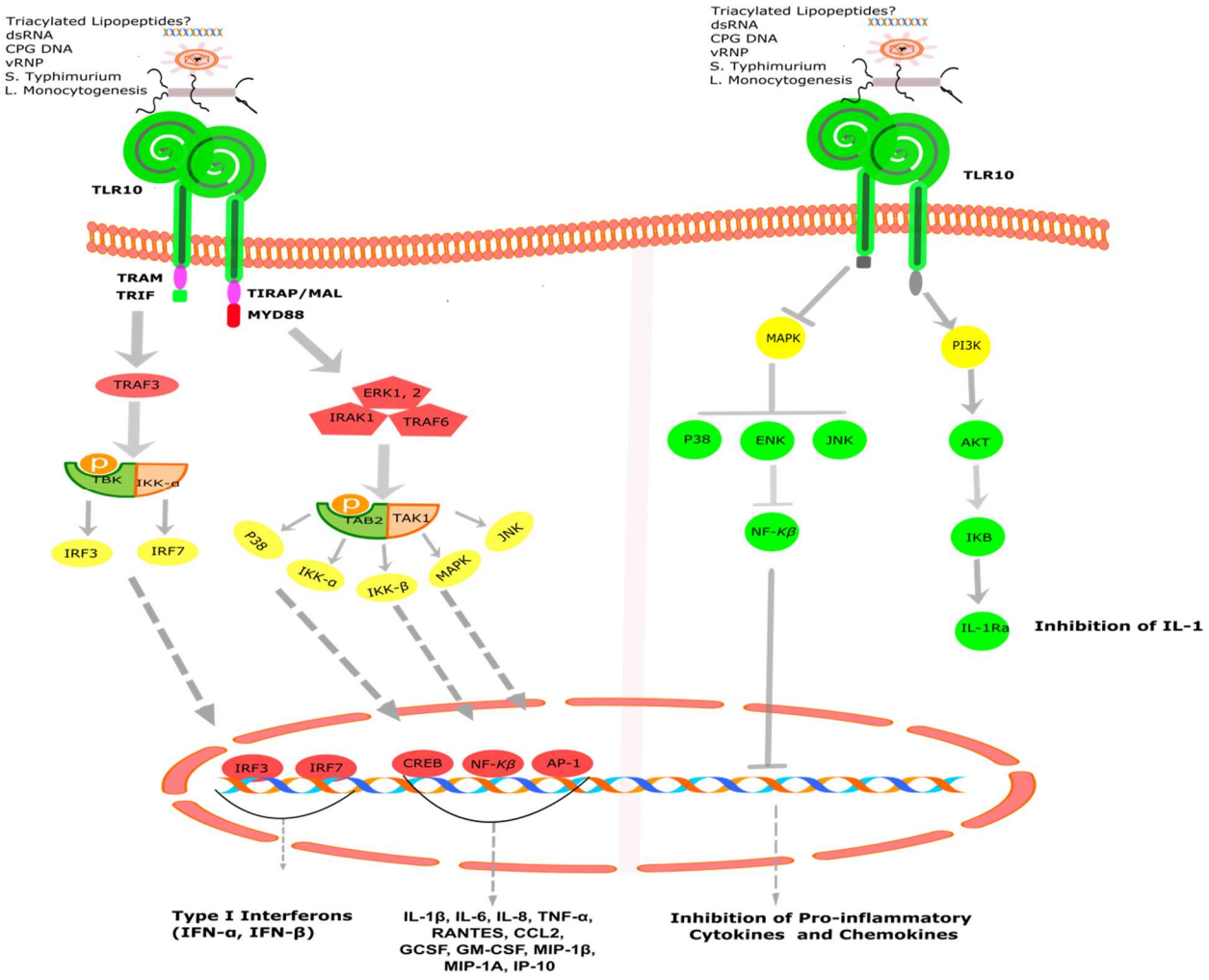

Figure 1. The Inflammatory and Anti-inflammatory Signaling Pathways of TLR10. Occupation of TLR10 by its ligands (eg, CPG-DNA, and dsRNA) initiates downstream signaling pathways via activation of adaptor molecules (eg, MYD88) and transcriptional factors such as NF-*kB and AP-1* which lead to the production of proinflammatory cytokines and chemokines (left). On the other hand, binding of TLR10 to the diverse ligands may inhibit MAPK downstream signaling or may activate PI3K (Right), which in turn inhibits the production of inflammatory mediators and production of IL-1Rα, an IL-1 receptor antagonist respectively.

Controversially, it is reported that production of proinflammatory cytokines increases by blocking TLR10 in human monocytes [44]. The engagement of TLR10 promotes the production of IL-1Ra, an anti-inflammatory cytokine, through TLR10-MAPK-dependent pathways [46]. A modulatory function of TLR10 has been reported by Mulla et al who found that the expressed TLR10 on trophoblastic cells induced apoptosis through recruitment of caspase-3 [35]. Two proteins, SIGIRR (single immunoglobulin interleukin-1 receptor-related protein) and interleukin 1 receptor‑like 1 (ST2), have been shown to negatively regulate TLR signaling by sequestering the proximal adaptor MyD88 (4). Recent data demonstrated that knockdown of TLR10 by small hairpin RNA (shRNA) significantly upregulated the expression of IFN-β in response to poly immune complex (poly I: C) challenge. Also, blockage of TLR10 by neutralizing antibody

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increases TNF-a, IL-6, and IL-8 secretion after microbial stimulation (48). The coexpression of TLR10 with TLR2 in HEK293 cells, resulting in reduction of IL-8 after bacterial or synthetic triacylated lipopeptide Pam3CSK4 challenge (51). Oosting et al also proposed that the inhibitory effect of TLR10 on IL-8 production is mainly through an autocrine or paracrine mechanism by the induction of IL-1Ra (IL-1 receptor antagonist), an endogenous antagonist for IL-1ß signaling (52). The silencing of TLR10 by RNA interference method leads to significant reduction in IL-8, CCL1 and CCL20 in the macrophage cell line THP-1 (16). Surprisingly, both thymus independent (TI) and thymus dependent (TD) antibody production are suppressed in TLR10 knock-in mouse model. Also, knockdown of TLR10 has shown suppressive effects on inflammation in the prostate tissue and RWPE-1 cell via downregulation of phospho-NF-κB P65, IL-6, and IL-8 (53). The monoclonal antibody against TLR10 on surface of mononuclear cells is able to suppress the production of proinflammatory cytokine, IL-6 (54).

- **TLR10 associated with dieases**

The relationship between TLR10 gene polymorphisms and diverse diseases has been already reported (Table 1). Theresa Neuper et al. have shown that engagement of TLR10 signaling pathway following H.Pylori infection reduces the production of inflammatory cytokines and chemokines, such as IL1-β (55). Similar results from studies in Chinese and European populations have confirmed a significant relationship between nonsynonymous single nucleotide polymorphism (SNP) of TLR10 (rs11096957) and severity of hip osteoarthritis (3, 40, 56). A population bearing a rare SNP rs4129009 in TLR10, which leads to the change from isoleucine to valine in the TIR domain of TLR10, has a decreased risk for developing atopic asthma (31, 57). TLR10–TLR1–TLR6 gene cluster analysis in pateints with Crohn's disease (58) suggested that individuals with copies of TLR10GGGG, are more susceptible to Crohn's disease (59) (Table 1). Moreover, a study in New Zealander population has revealed that genetic variation in TLR10 may be associated with differences in susceptibility of Crohn's disease and clinical findings (60). Recently, it has been reported that individuals carrying TLR10 992T/A and 720A/C polymorphisms have no adequate immune response to Crimean-Congo hemorrhagic fever (61). On the other hand, Qiaoyan Xiang et al. have reportet that the variant haplotype GAG is accompanied by higher level of IL-1β, IFN-γ, TNF-α in children with pneumococcal meningitis (62). Moreover, TLR10 gene polymorphisms among Korean population is associated with thyroid-associated ophthalmopathy, Hashimoto's disease, and Graves' disease (63). Accordingly, another study has reported an effect of missense polymorphism of TLR10 in papillary thyroid carcinoma and tumor size in the Korean population (64). A distinct TLR10 mRNA expression profile was reported in mature B cell neoplasias, follicular lymphoma, multiple myeloma, Epstein Barr virus–transformed cell lines, and Burkitt lymphoma (5). Furthermore, similar to normal and activated B cells, this population expresses high levels of TLR10 in chronic lymphocytic leukemia (65). Ligation of TLR10 by PAMPs and ubiquitous inhaled

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allergen in early life has a role in increasing asthma susceptibility (66). Accordingly, A health study cohort revealed a significant association between physician-diagnosed asthma among European American populations. These findings have provided strong support for risk of asthma and TLR10 genetic variation (67). Also, studies have confirmed the relationship between variants of TLR10 and increased risk of prostate cancer (68) and nasopharyngeal carcinoma (69).

Table 1. The properties of Some variation of TLR10 and susceptibility to disease

	Author	Year	Polymorphism(s)	Population(s)	Outcome(s)
1	Korppi M	2013	Rs4129009	Finnish Post bronchiolitis patients	Association with asthma medication and asthma risk
2	Kizildag	2017	922TT/AA	Crimean Congo hemorrhagic fever patient	Three times greater risk of AA genotype than TT genotype in patients with CCHF
			922T/A & 2322A/G		Association with patient mortality
			922T/A &720A/C		Association with pathogenesis of CCHF disease
			922AA		Decreased susceptibility of CCHF disease
			720CC		Increased susceptibility of CCHF disease
3	Tongtawee	2018	Rs10004195	Thai population	Increased susceptibility to the pathogenesis of H. Pylori & gastric
4	Vrgoc	2018	Rs11096957	Osteoarthritis patients and 597 controls from Croatian population	The association of the major alele (T) with lower and the minor allele(c) with higher risk for acquiring hip OA Association of Genotype T/T with the protection to hip OA and genotype T/C with higher risk for acquiring hip OA
5	Won Kyoung	2014	Rs4129009	Korean AITD patients (Grave's disease, Hashimoto disease, thyroid associated ophthalmopathy)	Association with prostate cancer and asthma
			Rs 10004195		Association with IgA nephropathy
			Rs11466653		Association with small tumor size PTC in Korean population
6	Noulivirta et al.	2016	Rs4129009	Full-term hospitalized infants for bronchiolitis at the age less than 6 months.	Association of TLR10rs4129009 minor allele G with elevated total serum IgE and rs4129009 allele with atopy
7	Lazarus et al.	2004	Single nucleotide polymorphisms (SNPs)	Case control study European American with diagnosed asthma	Association between two SNPs and physician-diagnosed asthma
8	Mikacenic	2012	TLR10 genetic variation	Healthy Caucasian	A strong association between pam3CSK4-induced cytokines in inflammatory responses and genetic variation of the TLR1/6/10
9	Jielin Sun	2006		prostate cancer patients and controls group in Sweden	Association of one single-nucleotide polymorphism in IRAK4 (Interleukin-1 receptor-associated kinases 4), in combination with the high-risk genotype at TLR6-1-10, and a significant increased risk of prostate cancer
10	J.Liu	2011	TLR10 Rs4129009	Neonates born in the Munich, Germany.	Modified FOXP3 expression by TLR1 rs4833095 and trendwie by TLR10 rs4129009 after LpA and Ppg

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					stimulation
11	Heinzman A	2010		Genotyped polymorphisms in asthmatic children and controls	Observation of the significant effects for TLR10 and IL13 as well as for AMCase and IL4 Importance the corresponding pathways in the genetics of asthma.
12	Beena Mailaparambil	2010	TLR10 rs11096955	Infants born with a gestational age ≤ 28 at the tertiary neonatal center, Freiburg	Existence of the genetic risk factors in the development of bronchopulmonary dysplasia Genetic association with single polymorphisms within TNFα, TLR10, and vascular endothelium growth factor
13	Bouker KB	2007	A4396G	Breast cancer cell lines.	More frequency in breast cancer cell lines compared with the general population
14	Ana M.Matas-cobos	2015	Rs4129009	Acute pancreatitis patients / controls	No relationship between TLR polymorphism and AP incidence
15	Yen-ching chen	2007		Patients with prostate cancer and controls without prostate cancer	No association between genes clusters TLR6-TLR1-TLR10 and increased risk of prostate cancer
16	Camila De Barros Gallo	2017	Rs11096957	OSCC, LSCC, OLD, OLP, and OLL patients and healthy controls, from Spain.	No association with OSCC, LSCC, OLD, OLP, and OLL
17	Macarena Guirado	2012	TLR10 rs4129009	Patients with urothelial bladder cell carcinoma in Spain.	Significant differences in TLR10 (rs4129009) gene between different tumor infiltration stage
18	Silvia Torices	2016	I473T variant	Patients with rheumatoid arthritis / controls subjects	No association between 1473T variant and increased susceptibility to RA. A significant correlation between seropositive patients for anti-CCP and erosive disease

CCHF: Crimean Congo hemorrhagic fever; **OA:** Osteoarthritis; **AITD:** Autoimmune thyroid disease; **Oscc: O**ral squamous cell carcinoma; Lscc **:** Laryngeal squamous cell carcinoma; **OLD:** Oral lichenoid disease**; OLP:** Oral lichen planus **; OLL:** Oral lichenoid lesions

- **Discussion**

TLR10 is the new member of pattern-recognition receptor with an unspecified ligand and biologic function. Within the human TLR family, TLR1 and TLR6 are the most closely related to TLR10 (70). Hence, at first glance, TLR10 may have the same biological function as TLR1 and TLR6, whereas different investigations have controversially reported the inflammatory and anti-inflammatory properties for hTLR10. Some studies have disclosed TNF-α production in macrophages and B cells following the upregulation of TLR10 expression via MYD88 and NF-κB activation (65, 71). Moreover, H. pylori LPS ligation of TLR10 and TLR2 on the surface of HEK293 cells involves NF-κB and proinflammatory IL-8 and TNF-α production (72). In addition, induction of the TLR10 expression by oxidative stress in type-2 diabetes and obese patients leads to activation of MAPK/NF-κB signaling, which increases the production of proinflammatory cytokines/chemokine IL-23A and CCL-5 (73). On the other hand, induction of IL-1Ra following TLR10 involvement, is associated with impaired TLR10 function in Meniere disease, suggests an inflammatory function of TLR10 (74). However, the findings from study by Tim Regan et al have demonstrated that knockdown of TLR10 in the macrophage cell line THP-1 reduces IL-8, CCL20,

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and CCL1 (75). Overall, these data indicated the role of TLR10 in triggered inflammation responses . Oosting et al reported that TLR10-induced IL-8 production is inhibited by autocrine or paracrine effects of endogenous antagonist for IL-1β signaling, IL-1 receptor antagonist (IL-1Ra) (52). The anti-inflammatory aspect of TLR10 is inhibition of antibody production either thymus independent or dependent in TLR10 knock-in mouse model (54). Accordingly, production of proinflammatory cytokine, IL-6, is suppressed by monoclonal antibody against TLR10 in human monocyte cell line (42). Also, decreased IL-2 and IFN-γ production is reported by activate T cells co-cultured with TLR10 differentiated dendritic cells (42). The inhibitory and suppressive effects of human TLR10 are not fully surprising. Because the human TLR10 is a member of pattern recognition receptors and Toll/IL-1R family with well-defined inhibitory molecules (76). However, several key mutations within BB loop of the TIR domain of TLR10 may cause the inhibitory TLR signaling and anti-inflammatory properties (77, 78). Proinflammatory roles of TLR10 through ligation with live H5N1 flu virus infections, not heat-killed or UV-inactivated pathogens have been shown in a research conducted by Lee SM et al. They have been reported that knocking down TLR10 expression in THP-1 cell lines suppresses the production of proinflammatory cytokines (65). These findings suggest the increased proinflammatory cytokines and interferon following the overexpression of TLR10 by live Influenza virus infection (65). On the other hand, suppressing proinflammatory signaling pathways induced by antibody-mediated engagement of TLR10 leads to downregulation of proinflammatory cytokines. Also, the long-term ligation of TLR10 alone is also enough for the monocytes differentiation into dendritic cells, which is not capable of activating T lymphocytes cells (42). The TLR10 downstream signaling pathway is similar to other TLRs, including TIRAP, MyD88, TRIF, and TRIF related adaptor molecule (TRAM) (79), but the anti-inflammatory effects of TLR10 may be located in its intracellular structure. The activating or repressive role of TLR10 is related to several amino acids in the BB loop of this receptor. Recently, more TIR domain-containing proteins such as sterile alpha motif (46) and armadillo-motif–containing protein (80), ankyrin repeats-1 (81), and BCAP (B cell adaptor for PI3K) (82) have been described. Hence, studies have suggested a negative regulatory role through inhibition of MYD88/TRIF and PI3K/Akt signaling pathway (82, 83).

- **Conclussion**

The biological role of TLR10 has not yet been fully understood, and this may be due to the lack of identification of the ligand of this receptor. Recent studies have reported the suppressive role of TLR10 compared to its role in stimulating the inflammatory response which may be due to a series of adaptor proteins that have not been identified so far. Overall, the findings indicated that different genetic variations in TLR10 could affect the balance between inflammatory and anti-inflammatory responses. It can be concluded that this change may regulate the susceptibility to infection diseases or autoimmune disorders. In addition, the type and nature of antigen for instance ligation of TLR10 by live or killed infections may initiate pro-

or anti-inflammatory immune responses. There is a prospect for the development of novel immunotherapy strategies based on modulation of the function of TLR10. Nevertheless, comprehensive studies are needed to identify molecular and biological aspects of human TLR10.

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- **Conflict of interests**

The Authors declare that there is no conflict of interest

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