Sangdun Choi
Editor

Encyclopedia of Signaling Molecules

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TNF-Inducible Gene 14 Protein

► PTX3

TNF-Related Apoptosis-Inducing Ligand

▶ APO2L/TRAIL

TNFRSF12A

▶ Fn14

TNFRSF13a

▶ BAFF/BLyS Family

TNFRSF13b

▶ BAFF/BLyS Family

TNFRSF13c

▶ BAFF/BLyS Family

TNFRSF17

▶ BAFF/BLyS Family

TNFRSF5

▶ CD40

TNFSF10

▶ APO2L/TRAIL

Tnfsf12

▶ Tumor Necrosis Factor-Like Weak Inducer of Apoptosis (TNFSFS12)

TNFSF13a

▶ BAFF/BLyS Family

TNFSF13b

▶ BAFF/BLyS Family

Tnk2

▶ ACK1

TNNC1

▶ Cardiac Troponin Complex: Cardiac Troponin C (TNNC1), Cardiac Troponin I (TNNI3), and Cardiac Troponin T (TNNT2)

Tnni3

▶ Cardiac Troponin Complex: Cardiac Troponin C (TNNC1), Cardiac Troponin I (TNNI3), and Cardiac Troponin T (TNNT2)

Tnnt2

▶ Cardiac Troponin Complex: Cardiac Troponin C (TNNC1), Cardiac Troponin I (TNNI3), and Cardiac Troponin T (TNNT2)

TNRC8

▶ CASK

TnT

▶ Cardiac Troponin Complex: Cardiac Troponin C (TNNC1), Cardiac Troponin I (TNNI3), and Cardiac Troponin T (TNNT2)

TOB1 (TOB, Transducer of ERBB2)

▶ BTG/TOB

TOB2 (Transducer of ERBB2 2)

▶ BTG/TOB

TOLL

▶ TLR4 (Toll-Like Receptor 4)

Toll/Interleukin 1 Receptor-Like 4

▶ Toll-Like Receptor 2

Toll/Interleukin-1 Receptor Domain-Containing Protein

▶ Toll-Like Receptor Adaptor Protein Family Members

Toll/Interleukin-1 Receptor-Like Protein 3

▶ TLR5 (Toll-Like Receptor 5)

Toll-Interleukin 1 Receptor (TIR) Domain-Containing Adapter Protein

▶ Toll-Like Receptor Adaptor Protein Family Members

Toll-Interleukin-1 Receptor Domain-Containing Adapter Protein Inducing Interferon Beta

▶ Toll-Like Receptor Adaptor Protein Family Members

Toll-Like Receptor 2

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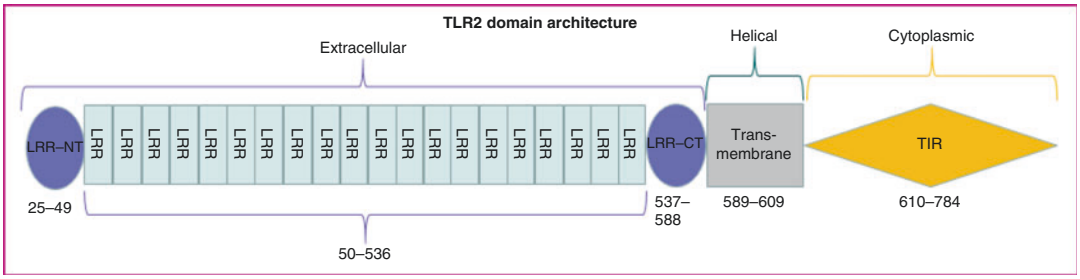
Synonyms

CD282; Cluster of differentiation 282; TIL4; Toll/interleukin 1 receptor-like 4

Historical Background

Toll-like receptors (TLRs) are expressed in immune cells such as dendritic cells and macrophages and recognize pathogens (Takeda and Akira 2005). Along with four other TLRs, human TLR2 was first named and reported as a receptor similar to the *Drosophila* Toll protein in 1998 (Rock et al. 1998). *TLR2* gene, with a size of 21,836 bases on chromosome 4, encodes the TLR2 protein. TLR2 is one of the pattern recognition receptors (PRRs) that sense pathogen-associated molecular patterns (PAMPs) of microbes and thus act as a first line of host defense (Janeway and Medzhitov 2002). The triggering of an innate immune response by PRRs after recognition of conserved microbial components and



Toll-Like Receptor 2, Fig. 1 TLR2 domain architecture. The ECD, transmembrane, and TIR domains of TLR2 including the LRR-N-terminal (LRR-NT) and LRR-C-terminal (LRR-CT) regions and their corresponding residues are shown

further development of the adaptive immunity were first described by Charles A. Janeway Jr. (Janeway 1989). The initial understanding of the TLR2 ligand was obtained in 1999 when a study revealed that TLR2 recognizes components of gram-positive bacteria, in contrast to TLR4, which binds to lipopolysaccharides of gram-negative bacteria (Takeuchi et al. 1999). A study first showed that danger-associated molecular patterns (DAMPs) also bind to TLRs and trigger inflammatory responses (Medzhitov and Janeway 2002). The dimerization mechanism of TLR2 with TLR1 or TLR6 for recognition of ligands and induction of cytokine production was first described in 2000 (Ozinsky et al. 2000). TLR2 participates in the myeloid differentiation primary-response protein 88 (MyD88)-dependent signaling pathway that is well known after several years of research aimed at identification of the currently known signaling molecules. The association of TLR2 with diseases was first reported in 2000, when the Bacillus Calmette–Guérin vaccine for tuberculosis was found to cause dendritic-cell maturation through TLR2 and TLR4 signaling (Tsuji et al. 2000).

Structure of TLR2

TLRs are type I transmembrane proteins that contain three types of domains: an N-terminal ligand-binding ectodomain (ECD) with leucine-rich repeats (LRRs), a transmembrane helix domain, and the Toll/interleukin (IL)-1 receptor (TIR) homology domain, which drives the TLR-related downstream signaling (Figs. 1 and 2a) (Botos et al. 2011). To date, crystal structures have been determined for the ECD of human TLR2 in the heterodimeric form with TLR1 and for cytoplasmic TIR domain of TLR2 in the monomeric form (Botos et al. 2011). Due to technical difficulties, the structure of the full-length TLR2 protein with all three domains has not been solved. The ECDs of TLRs 1, 2, 4, and 6 have a horseshoe-like structure similar to that of TLR3 and TLR5, but in the LRR superfamily, these TLRs belong to an "atypical" subfamily, whereas TLR3 and TLR5 are members of the "typical" subfamily (Jin et al. 2007). The ECD of atypical LRR subfamily members contains N-terminal, central, and C-terminal subdomains. An overlapping structural organization is evident in typical TLRs and TLR2 because the N-terminus of TLR2 contains the LRR N-terminus and 1–4 LRR motifs, with LRR modules consisting of 24 amino acid residues, an asparagine ladder, and a phenylalanine spine (Jin et al. 2007). Unlike typical LRRs, the central and C-terminal domains of TLR2 have LRR units with 20–30 residues, and their β-sheet arrangements are different (Jin et al. 2007). Moreover, the central subdomain is lacking the asparagine ladder and phenylalanine spine (Jin et al. 2007). In contrast to typical TLRs, which recognize ligands in their concave surface, ligands of TLR2 bind to the convex surface of the ECD (Botos et al. 2011). LRR positions 9–12 are filled with hydrophobic residues where the ligand is recognized. Just as other known TIR domains, TLR2 TIR domain contains a central 5-stranded β-sheet surrounded by 5 α-helices

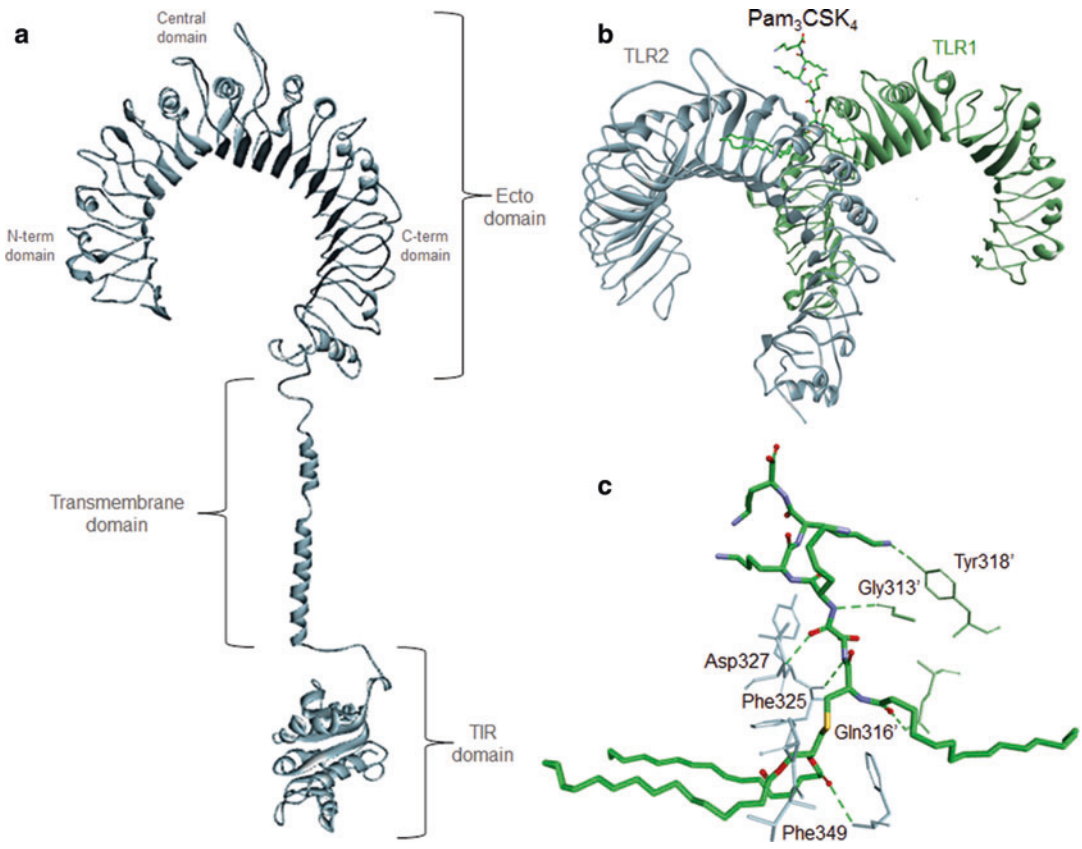
(Botos et al. 2011). The BB-loop that joins the βB strand and αB helix is crucial for heterodimerization of TLR2 with its partner (Botos et al. 2011). The amino acids from the DD-loop, which bridges the βD strand and αD helix, and αC helix also participate in dimerization. The P681H mutation in the BB loop of human TLR2 prevents the TIR–TIR interactions with MyD88 and abrogates the signal transduction (Botos et al. 2011). This observation proves the significance of residue 681 and the BB-loop in TLR2 signaling.

Ligand Recognition by TLR2

TLRs from vertebrates can be subdivided into six subfamilies based on evolution and the type of ligands they recognize. They are TLR1/2/6/10, 3, 4, 5, TLR7/8/9, and TLR11/12/13/21/22/23 (Roach et al. 2005). The members that are expressed on the cell surface are TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11. TLR2 mainly recognizes lipopeptides that are mostly expressed on the external membrane of gram-positive bacteria. TLR2 binds to a wide variety of ligands from several species of pathogens to initiate TLR2 signaling that induces cytokines (Oliveira-Nascimento et al. 2012). The ECD of TLR2 can sense ligands from several microbes, and they include lipopeptides, lipoteichoic acid (LTA), glycosylphosphatidylinositols (GPIs), and phospholipomannan. DAMPs released by dying cells or during a disease can activate TLRs, and these receptors may play a protective role or cause immune disorders. To bind to the cognate ligand, TLR dimers bind to cofactors that help to deliver the appropriate ligand to TLRs. TLR2 in association with coreceptors such as cluster of differentiation (CD) 36 and CD14 recognize a few ligands but not all (Lee et al. 2012). The innate immune responses to the TLR2 ligands LTA and R-macrophage-activating lipopeptide 2 (MALP2) are improved by CD36. Tumor necrosis factor (TNF)-α production triggered by several TLR2 binders is associated with CD14. Other accessory molecules that facilitate TLR2 ligand detection include guanyl nucleotide−releasing protein 94, integrin, dectin-1, and chemokine receptor type 4 (Lee et al. 2012). DAMPs are also recognized by TLR2, in particular, versican, high-mobility group box (HMGB) 1, pancreatic adenocarcinoma upregulated factor, amyloid β, α-synuclein, serum amyloid A, synaptosome-associated protein, and β2-glycoprotein I (van Bergenhenegouwen et al. 2013). The recognition of Pam_3CSK_4 by human TLR2-TLR1 has been analyzed by X-ray crystallography, and these data provide a detailed picture of atomic interactions between human TLR2 and its ligand (Fig. 2b and c). In addition, Pam_2CSK_4 with two acyl chains induces heterodimerization of mouse TLR2 with mouse TLR6; this process was also analyzed by X-ray crystallography. For TLR2, both available crystal structures with agonists show conserved interactions of TLR2 with Asp327 and Phe349, but these interactions are absent in the complex of TLR2 with *Streptococcus pneumoniae* LTA (pnLTA) or with phosphatidylethanolamine-diethylene triamine penta-acetic acid (PE-DTPA); these complexes fail to activate TLR2 signaling because of the special binding mode (Kang et al. 2009). After these two diacyl lipopeptide ligands bind to the TLR2 monomer, oxygen atoms in the head group of the ligand repel the hydrophobic sulfur site in TLR2, shifting the head group to a position that differs from that observed in lipopeptides (Kang et al. 2009). This head group rotation disrupts hydrogen bonding between the peptide head group, Asp327 and Phe349, thus inhibiting heterodimerization of TLR2 with TLR1 or TLR6, which is essential for activation of TLR2 signaling.

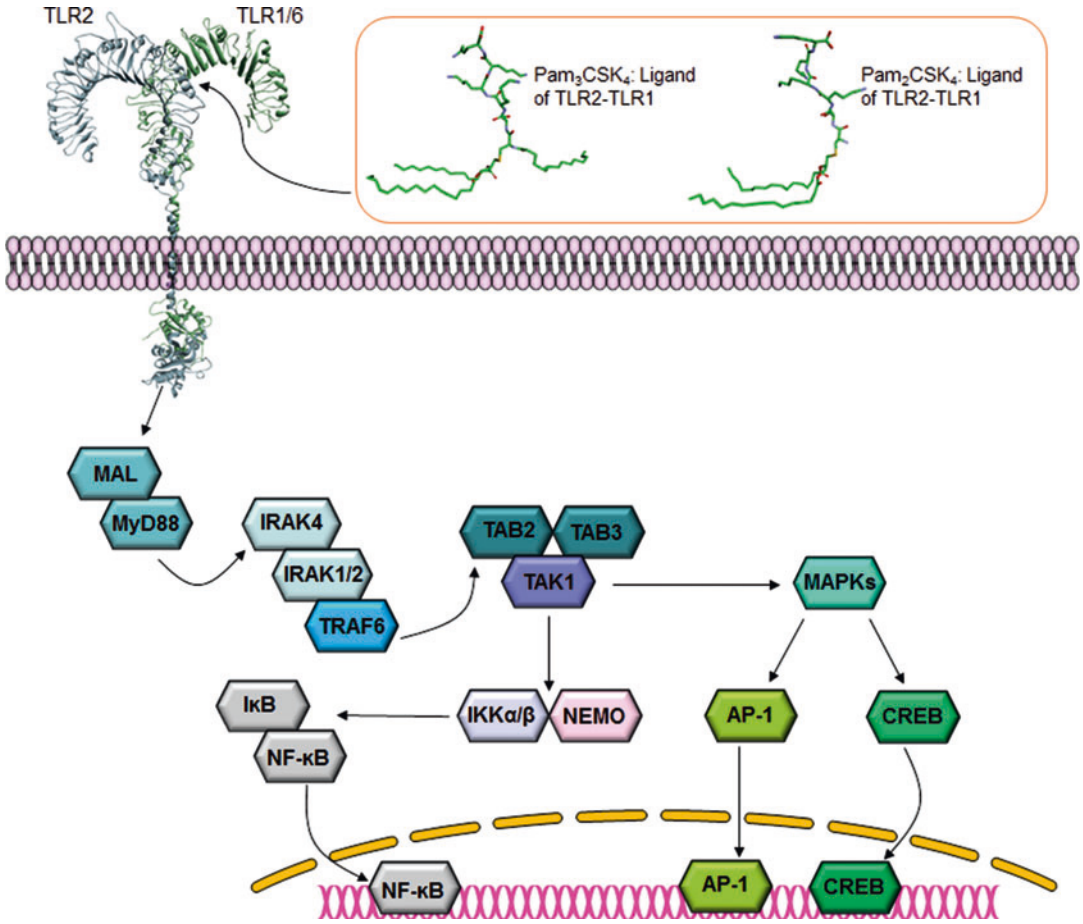
MyD88-Dependent TLR2 Signaling

Ligand-induced dimerization of ECDs of TLR2 subfamily members subsequently leads to dimerization of their TIR domains and initiation of downstream signaling to induce the genes related to innate immunity (Takeda and Akira 2004; Gay et al. 2014). An overview of MyD88-dependent TLR2 signaling is shown in Fig. 3. Activated TLRs bring the C-terminus of two ECDs that are connected to the transmembrane helix closer to each other. Knowledge on the role of



Toll-Like Receptor 2, Fig. 2 Structural arrangements of TLR2 and its ligand recognition in association with TLR1 (**a**) A three-dimensional (3D) representation of the three domains of TLR2 including the N-terminal, central, and C-terminal domains of ECD. We modeled the complete TLR2 structure of all three domains on the basis of the available resources using Modeller v9.14 and Accelrys Discovery Studio 4.0. (**b**) Recognition of Pam_3CSK_4 by the TLR2-TLR1 heterodimer via residues in LRRs 9–12 region. (**c**) The TLR2-TLR1–Pam_3CSK_4 complex. The TLR2 and TLR1 residues are shown in *blue* and *green*, respectively. Carbon, nitrogen, and oxygen atoms of Pam_3CSK_4 are highlighted in *green*, *blue*, and *red*, respectively. *Apostrophes* represent TLR1 residues

transmembrane α-helices in the TIR domain dimerization of TLRs is limited. TLR2 participates in the MyD88-dependent canonical pathway that is activated by every TLR except for TLR3. TLR2 signaling starts with TIR–TIR interactions with MyD88 that involve the bridging adaptor protein MyD88 adaptor-like protein (MAL; also known as TIRAP). Subsequently, IL-1-receptor–associated kinase (IRAK) 4 and MyD88 interact through their death domains (DDs) (Takeda and Akira 2004). Thereafter, IRAK1 or IRAK2 is recruited and phosphorylated by IRAK4 including its autophosphorylation (Takeda and Akira 2004). The phosphorylated IRAK2 or IRAK1 is then released from the complex and binds to tumor necrosis factor receptor–associated factor 6 (TRAF6) (Takeda and Akira 2004). TRAF6 interacts with the transforming growth factor β–activated kinase 1 (TAK1)-binding protein (TAB) 2 and TAB3 to activate the TAK1 complex. TAK1 activates nuclear factor of kappa light polypeptide gene enhancer in the B-cell inhibitor (IκB) kinase (IKK) complex including nuclear factor κB (NF-κB) essential modifier (NEMO), the component necessary for regulation of the IKK complex (Takeda and Akira 2004). This complex phosphorylates IκB to release NF-κB to initiate the transcription of proinflammatory genes. TAK1 can also activate the mitogen-activated protein kinase (MAPK) pathways



Toll-Like Receptor 2, Fig. 3 An overview of TLR2 signaling. To protect the host, TLR2 binds to TLR1 or TLR6 depending on the type of ligand to initiate MyD88-dependent downstream signaling and induces production of cytokines, and thereby, to combat harmful microbes. The description of the entire pathway is given in the section "MyD88-dependent TLR2 Signaling"

through phosphorylation of MAPKs, which then activate the transcription factors such as activator protein 1 (AP-1) and cyclic adenosine monophosphate responsive element-binding protein (CREB), which drive transcription of cytokine genes (Gay et al. 2014). These cytokines include TNF-α, IL-1α, IL-1β, IL-6, IL-8, and IL-12. Evidence for the induction of IRF7 proves that TLR2 is also capable of regulating the production of type 1 interferon (IFN) (Bauernfeind and Hornung 2009). TLR2-induced cytokines and type 1 IFN participate in the fight against infectious microbes (in defense of the host). In contrast, surplus activation of TLRs results in various innate immune diseases. Hence, negative regulation of TLR signaling is required, and TLR ligands mainly play this role by recruiting negative regulators (Kondo et al. 2012). In TLR2 signaling, molecules such as cylindromatosis, a tumor suppressor that is induced during activation of TLR2, inhibit the signaling (Kondo et al. 2012). Peptides derived from human immunodeficiency virus 1 gp41 have been shown to inhibit TLR2 activation induced by LTA in macrophages, and this effect was assessed by measurement of TNF-α secretion. There are also a few synthetic antagonists available for the control of TLR2 signaling.

The Role of TLR2 in Diseases

Genetic variations in humans have clarified the role of TLRs in infectious and autoimmune diseases. The outcomes due to single nucleotide polymorphisms in genes encoding TLR2 and the molecules that are essential for TLR2 signaling are known to cause serious diseases and some are discussed below. The G2258A polymorphism in TLR2 reduces the ligand-induced TLR2 activation and increases the risk of asymptomatic bacteriuria in females (Medvedev 2013). The R753Q polymorphism in TLR2 poses a risk of sepsis, atopic dermatitis, and tuberculosis (Medvedev 2013). Deletion of nucleotides between positions −196 and −174 in the promoter region of the *TLR2* gene may be involved in carcinogenesis and can increase the risk of prostate and cervical cancer among North Indians (Medvedev 2013). A rare TLR2 polymorphism, P631H, is believed to be associated with systemic sclerosis, tuberculosis, and progression of pulmonary arterial hypertension (Medvedev 2013). Patients infected with *Trypanosoma cruzi* who have the S180L polymorphism in MAL show poor ligand-induced TLR2 signaling, which inhibits the progression of Chagas disease (Ramasawmy et al. 2009). Apolipoprotein-CIII activates monocytes via TLR2 and contributes to atherosclerosis, whereas TLR2 knockout mice show reduced atherosclerosis; one or more TLR2 DAMP agonists that are released in cells other than bone marrow cells are known to cause TLR2-promoted atherosclerosis (Yamashita et al. 2006). TLR2 expression is stronger in various cells of patients with rheumatoid arthritis (RA), and rodents treated with the streptococcal cell wall develop joint swelling that is TLR2 dependent. HMGB1, a TLR2 DAMP, is involved in the pathogenesis of RA (Keogh and Parker 2011). Serum amyloid A, another TLR2 DAMP that is expressed more actively in RA patients, may also be involved in the initiation or progression of RA (Keogh and Parker 2011). TLR2 expression in monocytes is increased in patients with autoimmune diabetes; this observation indicates that TLR2 may initiate this disease by recognizing β-cell death (Keogh and Parker 2011). OPN-305 is an antiTLR2 antibody that was found to be effective against ischemia-reperfusion injury in pigs (Arslan et al. 2012). T2.5 (an antiTLR2 antibody) prevents sepsis in mice during coadministration with 1A6 (an antiTLR4 antibody) (Lima et al. 2015).

Summary

TLR2 has been implicated in several infectious diseases and autoimmune disorders, and hence targeting of TLR2 through modulators to either activate or inhibit its activity can have therapeutic benefits. Accumulating evidence on TLR2 expression and TLR2-induced cytokine production during some diseases proves the role of TLR2 in initiation or progression (or both) in these pathologies. Targeting TLR2 alone should be more beneficial than targeting the molecules involved in TLR2 signaling because the latter approach may lead to needless inhibition of cytokines induced by other TLRs. Several diseases involve both TLR2 and TLR4; thus, the understanding of the molecular mechanisms underlying the pathological role of TLR2 and other TLRs in a particular disease will help to design inhibitors or activators accordingly. The knowledge about all the TLRs involved in a particular innate immune disorder can help to identify a single inhibitor that targets multiple TLRs. Rather than developing synthetic high-molecular-weight compounds targeting TLR2, it is more rational to design drug-like and peptidomimetic compounds that have suitable pharmacokinetic and pharmacodynamic properties. Similarly, screening of natural compounds to identify TLR2 modulators is also effective. Molecules that modulate TLR2 signaling or exert their effects through direct binding to TLR2 are scarce. Hence, more studies on the structure–activity relation are needed to modify and increase the efficiency of the existing TLR2 modulators in addition to the effort to discover molecules with different chemical structures.

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Toll-Like Receptor 3

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Synonyms

CD283; CD283 antigen