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Research Article

TOLL-LIKE RECEPTORS: THE GATEWAY OF IMMUNE SYSTEM

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ABSTRACT

The innate immunity plays a critical role in the protection of host against pathogens and includes a wide variety of cellular receptors as its key component called Pattern recognition receptors (PRRs) which recognize the highly conserved molecules that are exclusively expressed by large classes of microorganisms. Toll-like receptors (TLRs), the most extensively studied PRRs play a vital role in maintaining periodontal health and hence over exaggerated or chronic signaling during inflammation could lead to the destruction of periodontal tissues. Targeting the components of TLR signalling cascades could lead to novel therapies in the treatment of these various inflammatory and infectious diseases as well as cancer. This review provides a novel insight about the history, structure, signaling and role of TLRs in the pathogenesis of various diseases emphasizing their role in periodontal health and disease and their application as therapeutic targets in the treatment of these disease processes.

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INTRODUCTION

Periodontitis is defined as an infection driven chronic inflammatory disease that affects the integrity of tooth supporting tissues.¹The extent and severity of the periodontal tissue destruction mainly depends on the dynamic host-microbial interactions and hence the knowledge of host immune system which includes Toll-like receptors (TLRs) as one of its key components is essential for better understanding of the disease process.² The innate immunity plays a critical role in the host protection against pathogens and includes a wide variety of cellular receptors as its key component called Pattern recognition receptors (PRRs) which recognize the highly conserved molecules that are exclusively expressed by large classes of microorganisms.^{3,4,5}

Among the PRRs, TLRs are the most extensively studied group of receptors which are evolutionarily conserved molecules from flies to humans.⁶ Since the discovery of Toll gene in *Drosophila* in the late 1980s and its mammalian homologue in the late 1990s has contributed a lot in reshaping our understanding of the immune system.⁷ Toll-like receptors (TLRs) recognize the conserved molecular patterns on the microbial pathogens called Pathogen associated molecular patterns (PAMPs) and also recognize an array of endogenous molecules called "danger signals" or Danger associated molecular patterns (DAMPs).⁸ Thus TLR ligation

initiate the intracellular signalling cascades resulting in the release of various biologically active molecules such as cytokines, costimulatory molecules, etc which subsequently initiate and modulate the adaptive immune response and therefore linking the innate and adaptive immunity.⁹TLRs play a critical role in the homeostasis of the immune system and over exuberant or inadequate control of TLR signalling and genetic variations in TLR genes may contribute to the pathogenesis of various immune and inflammatory disorders like rheumatoid arthritis, sepsis, allergy and periodontitis¹⁰ and also play a role in the development of cancer.¹¹

History of TLRs

Christiane Nusslein-Volhard in the year 1985 discovered Toll receptor in *Drosophila melanogaster* commonly called as fruit fly.¹² The role of Toll in the immunity of *Drosophila melanogaster* was identified by Jules A Hoffman *et al* in the year 1996.^{13,14,15} Ruslov Medzhitov and Charles Janeway identified the homologues of *Drosophila* toll in mammals in the year 1997 and named it as human toll, which was later named as Toll-like receptor4 (TLR4).¹⁰ In 1998, Anderson explained the embryonic Toll signalling pathway in *Drosophila* and Bruce Beutler and colleagues demonstrated the role of TLRs in the recognition of microbial ligand, lipopolysaccharide in mice.^{12,16,17} Subsequently the other members of TLR family

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and their ligands were also identified and till date 13 TLRs have been identified in mice and 11 in humans.¹⁰

Various other PRRs are Nod like receptors [NLRs] (nucleotide binding oligomerization domain like receptors) RIG like receptors [RLRs] (retinoic acid inducible gene like receptors) C type lectin receptors, Cytosolic DNA receptors, Peptidoglycan recognition proteins(PGRP),etc^{18,19,20}

Structure of TLRs

TLRs are transmembrane glycoproteins which comprises of extracellular domain, transmembrane domain and Cytoplasmic (intracellular) domain (Fig. 1).¹³ The extracellular domain comprises of 16-28 Leucine rich repeats (LRRs). The LRR family contains approximately 6000 proteins.¹⁰ The LRR family protein consists of multiple LRR modules.^{21,22} The individual LRR module is 20-30 amino acids long and are characterized by conserved pattern of hydrophobic residues.¹⁹ A single transmembrane α -helix bridges the extracellular and cytoplasmic domain and play an important role in receptor activation.¹⁶ The cytoplasmic domain (TIR domain) is composed of common fold containing a five stranded parallel β sheets surrounded by five α -helices. The role of second β -sheet and the second α -helix is essential in TLR dimerization and/or adaptor recruitment.¹⁹ The TIR domain plays a vital role in protein-protein interaction. Certain specific adaptor molecules play a vital role by participating in the signalling pathway through the TIR domains.^{10,13}

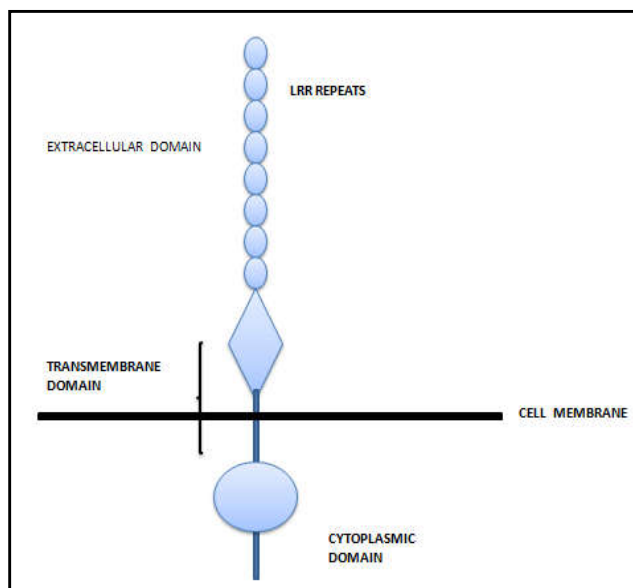


Figure 1 Structure of TLRs

Classification of TLRs

Based on primary structure and function, TLRs are subdivided into 5 subfamilies TLR2, TLR9, TLR3, TLR4 and TLR5 subfamilies. TLR2 subfamily comprises of TLR1, TLR2, TLR6 and TLR10. TLR9 subfamily comprises of TLR7, TLR8 and TLR9. TLRs 3,4 and 5 work alone as a single member or in combination with other receptors or molecules.³ Based on location, TLRs are classified as cell surface(TLR1,2,4,5,6) and Intracellular TLRs(TLRs 3,7,8,9).¹⁰

TLRs and Their Ligands

Table 1 TLRs and Their Ligands (PAMPs)

TLRs	LIGANDS(PAMPs)
TLR1	Triacyl lipopeptides
TLR2	Lipoprotein/lipopeptides, Peptidoglycan/lipoteichoic acid Mycobacterial lipoarabinomannan, Zymosan Porphyromonas gingivalis lipopolysaccharide, fimbriae Bacteroides fragilis lipopolysaccharide Capnocytophaga ochracea lipopolysaccharide
TLR3	Double-stranded RNA, Polyinosine-polycytidylic acid
TLR4	Escherichia coli lipopolysaccharide Porphyromonas gingivalis lipopolysaccharide Actinobacillus actinomycetemcomitans lipopolysaccharide Fusobacterium nucleatum lipopolysaccharide
TLR5	Flagellin
TLR6	Peptidoglycan/lipoteichoic acid, Diacyl lipopeptides, Zymosan
TLR7	Imidazoquinoline
TLR8	Single-stranded RNA, Imidazoquinoline
TLR9	Bacterial DNA, CpG oligodeoxynucleotide
TLR10	Not determined

The extracellular domain of TLRs sense a broad range of molecules that are present on the pathogenic bacterial, protozoan, viral and fungal organisms called the pathogen associated molecular patterns (PAMPs) or the endogenous danger molecules called the damage associated molecular patterns (DAMPs) and these constitute the ligands of TLRs.^{10,15} (Tables 1,2)

Table 2 TLRs and Their Ligands (DAMPs)

DAMPs	Associated TLRs
HMGB1	TLR2,4,9
HSP	TLR2,4
Hyaluronan	TLR2,4
Heparan sulfate	TLR4
DNA	TLR9
Biglycan	TLR 2,4

TLR Signalling

TLRs recognize a large number of ligands and the signalling pathways following the ligand binding differ from one another. On the whole the TLRs dimerize and go through conformational changes so as to recruit adaptor molecules through the TIR domain.³ The five adaptor proteins involved in TLR signalling are Myeloid differentiation factor 88 (MyD88), MyD88 adaptor like (MAL) or TIRAP, TLR-related adaptor protein inducing interferon (TRIF), TRIF-related adaptor molecule (TRAM) and Sterile alpha and armadillo motif containing protein (SARM).³

TLR signalling cascades are separated into two groups - MyD88 dependent pathway and MyD88 independent pathway.²² Most TLRs use MyD88 dependent pathway except TLR3 which utilizes the MyD88 independent pathway.³ TLR4 utilizes both these pathways and the preference between these two pathways may be accredited to the smooth and rough forms of LPS.³

TLR ligation triggers the interaction between TIR domain and cytoplasmic adaptor molecules which activates IL-1 receptor associated kinase (IRAK) which then associates with tumor necrosis factor receptor associated factor 6 (TRAF6) resulting in the activation of two distinct pathways in which one results in the stimulation of activator protein 1 (AP-1) through mitogen activated protein kinase (MAK).⁷ The other pathway results in the

stimulation of transforming growth factor β activated kinase-1-binding protein complex (TAK1) which improves the activity of inhibitor of nuclear factor $\kappa\beta$ kinase which in turn degrades the inhibitor of NF- $\kappa\beta$ resulting in the release of NF- $\kappa\beta$. The AP-1 and NF- $\kappa\beta$ stimulate the expression of inflammatory genes and hence the release of cytokines like TNF α , IL-1, IL-6, IL-12, IL-8 and costimulatory molecules like CD 80 and CD 86.^{7,14,20} The MyD88 independent pathway is governed by TRIF which activates the transcription factors interferon regulatory factors 3 and 7 (IRF3 and IRF7). This in turn induces the production of type 1 interferons and hence closely linked to anti-viral signalling (Fig. 6).^{3,7}

Expression of TLRs

Toll-like receptors are chiefly expressed by the cells of the innate immune system that includes neutrophils, monocytes/macrophages and dendritic cells which provoke a broad range of immune responses to specific pathogens.¹³ Neutrophils utilizes the pertinent TLR(1,2,4,5,6,7,8,9,10)⁷ and macrophages/monocytes express TLR(1,2,4,5,6,7,8). Dendritic cells, the professional antigen presenting cells, B and T lymphocytes also express TLRs.^{23,24} (Table 3)

Cells of the periodontium also express TLR in addition to the immune cells. Investigations have shown the expression of TLR2, 6 and 9 from human gingival epithelial cells and also low levels of TLR4. Human gingival fibroblasts express TLR 2,3,4 and also the related molecules CD14 and MD 88.⁷ The PDL fibroblast express TLR2 and 4, CD 14, MD-2 and MyD-88 and investigations have shown a relatively weaker expression of CD14 and a stronger TLR-2 expression than the human gingival fibroblasts.⁷(Table4)

Table 3 Expression of TLRs in Immune Cells

IMMUNE CELLS	TLRs
Neutrophils	TLR 1,2,4,5,6,7,8,9,10
Monocytes/macrophages	TLR 1,2,4,5,6,7,8
Myeloid dendritic cells	TLR 1,2,3,4,5,6,7,8,10
Plasmacytoid dendritic cells	TLR 1,6,7,9
B lymphocytes	TLR 1,3,6,7,9,10
T lymphocytes(Th1/Th2)	TLR 2,3,5,9
T lymphocytes(regulatory)	TLR 2,5,8

Table 4 Expression of TLRs in Periodontal Cells

Periodontal Cells	TLRs
Gingival epithelial cells	TLR 2,3,4,5,6,9
Gingival fibroblasts	TLR 2,4,9
Endothelium	TLR 1,3,4,5
Osteoblasts	TLR 1,4,5,6,9
Osteoclasts	TLR 2,4
Cementoblast	TLR 2,4
Periodontal ligament fibroblasts	TLR 2,4

TLRs In Innate And Adaptive Immunity

TLRs form the major component of the innate immune system by playing an essential role in recognising the pathogen associated molecular patterns and initiate the immune response and also promote the adaptive immune response.^{14,6} Neutrophils, monocytes/macrophages and dendritic cells which are the major cells of the innate immune system express different Toll-like receptors.⁷ Activation of TLR signalling pathway by the binding of TLR with the respective ligands

result in the increased production of pro-inflammatory cytokines, chemokines and interferon production.^{18,25} Triggering of the innate immunity is followed by the induction of adaptive immunity, the most sophisticated system to combat micro organisms in which B and T lymphocytes express antigen receptors on the surface and help in detecting the foreign antigens. Triggering of the B and T lymphocytes by the antigens result in clonal expansion which accounts for the immunological memory.⁴

The microbial components bind with the Toll like receptors that are expressed by the immature dendritic cells and in turn the dendritic cells are activated and get matured and present the pathogen derived antigen. This results in the expression of co-stimulating molecules and inflammatory cytokines which interact with the naive T cells and trigger the adaptive immune response.⁴ Naive human B-cells express only low levels of TLR where as memory B-cells are more reactive and more prone to proliferate and differentiate upon TLR stimulation by expressing significant levels of TLRs like TLR 1,6,7,9,10 and low levels of TLR2.²⁶

TLRs were suggested to influence the development and survival of B-cell subsets through TLR induced type1 interferons. Activation of NF- $\kappa\beta$ transcription factor by TLRs is thought to be enough to stimulate the expression of Blimp-1 which is a transcription factor that is important for plasma cell and preplasma memory B-cell differentiation. The main feature of competence of TLRs to stimulate adaptive immunity is by the upregulation of MHC antigen presentation and co-stimulatory molecules such as CD80 and 86, which in turn stimulate the antigen specific T-cell response.²⁶

Negative Regulation of TLRs

Overexpression or insufficient control of TLRs can result in potentially deleterious effect which may be due to the poor functioning of negative regulators of TLR signalling. Hence the negative regulators of TLR work at various levels of TLR signalling pathway and be vigilant on the intensity and duration of TLR responses and hence avert the overexpression of TLRs.²⁷ Various mechanisms that are involved in the negative regulation of TLRs are monoclonal antibody blockade, natural or synthetic antagonists, soluble decoy receptors, transcriptional regulation, BB loop decoy peptides, dissociation of adaptor complexes, kinase inhibitors and pathogen evasion.^{1,10}

TLRs in Periodontal Health

An activated and controlled inflammatory state of innate immune defence system is seen in clinically healthy periodontal sites with an organized expression of innate host defence mediators. These immune mediators in healthy tissues assist in the passage of neutrophils from the gingival tissue and form a barrier in the gingival crevice and thus the oral health is maintained.²⁸ Different types of TLRs are expressed by the periodontal tissues in response to the commensal and pathogenic oral microorganisms present in the dental plaque.¹³ A low level of TLRs are expressed by the healthy gingival tissues in response to the oral commensal bacteria in order to maintain a controlled inflammatory state.²⁸ Thus the TLRs play a vital role in the innate immunity which is the first line of defense and thus helps in maintaining the periodontal health.¹³

TLR signalling prevents the invasion of both the commensal and pathogenic microorganism into the periodontal tissue through the release of anti-bacterial β -defensins, cathepsins and calprotectin as well as the neutrophil chemoattractant (IL-8) and thus maintains the periodontal health. An optimal balance between the pro-inflammatory and anti-inflammatory mediators is brought about by the anti-inflammatory mechanisms in periodontal health and thus preventing the inflammation.¹³

TLRs in Periodontal Disease

In health, low amounts of gram positive aerobes and facultative anaerobes like species of streptococcus and actinomyces are found supragingivally. In periodontal disease, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* and *Tannerella forsythia* are found frequently in deep pockets. These pathogens stimulate the TLRs continuously resulting in the overproduction of pro-inflammatory mediators and hence the homeostasis of the mediators seen in the periodontal health is disrupted. The periodontal pathogens invades the gingival epithelial barrier and then into the deeper tissues and thus activating TLRs in other cells like macrophages, fibroblasts, osteoblasts and antigen presenting cells resulting in further increase in the production of pro-inflammatory cytokines.¹³

Epithelial cells of the gingival sulcus are the first cells to react to PAMPs resulting in the expression of ICAM-1 and the ligand for lymphocyte function associated antigen-1 (LFA-1), interleukin-8 (IL-8) and matrix metalloproteinases (MMPs). ICAM-1 and ligand for LFA-1 are associated with the attachment and migration of leukocytes towards the gingival sulcus. IL-8 aids in neutrophil migration and the MMPs which are a group of endopeptidases cause tissue destruction directly by degrading the extracellular matrix and basement membrane components.^{13,28}

These epithelial cells in turn activate the other resident and non resident cells. Activation of TLRs lead to increased neutrophil chemotaxis and production of pro-inflammatory mediators IL-1, IL-6 and TNF- α which play a vital role in the triggering of bone resorption and tissue degrading proteinases and in turn result in periodontal tissue destruction.¹³

The endothelial cells lining the blood vessel are triggered by IL-8 which is secreted by TLR4 induced epithelial cells and hence an increased expression of ICAM-1, E-selectin and VCAM-1. These adhesion molecules in turn results in increased adhesion of monocytes. PAMPs stimulate TLRs in monocytes and result in the differentiation of monocytes into osteoclasts with the help of receptor activator of nuclear factor- κ B ligand (RANKL).¹³

Stimulation of TLRs in dendritic cells which are the resident immune cells present in both the epithelium and connective tissue result in the maturation of these dendritic cells which not only function as antigen presenting cells but also lead to the release of cytokines and co-stimulatory molecules. These in turn stimulate T-lymphocytes to exert a Th1 or Th2 immune response. Stimulation of gingival fibroblasts lead to tissue destruction by the release of pro-inflammatory cytokines. Activation of TLRs in periodontal ligament fibroblasts by the PAMPs also result in tissue degradation by the production of proteinases.¹³

The invasion of the PAMPs in the circulation result in T-cell differentiation and production of antibodies by plasma cells derived from B-lymphocytes. PAMPs stimulate TLRs in osteoblast resulting in the production of MMPs and Prostaglandin E₂ and hence cause bone resorption. RANKL is expressed by osteoblasts, marrow stromal cells, T and B cells. RANKL activates osteoclasts and their precursors by binding with receptor activator of nuclear factor- κ B (RANK) in the presence of macrophage colony stimulating factor (M-CSF). If the destructive process is unchecked, it will result in the loss of attachment and loss of alveolar bone.^{7,13}

Periodontopathogens and TLRs

Increased expression of TLRs by immune cells and cells of the periodontal tissues is seen in response to the elevated levels of periodontal pathogens through the recognition of PAMPs.^{29,30} Studies have displayed that *P.gingivalis* lipid A species such as the triacylated and pentaacylated lipids stimulate the cells in TLR4 dependent manner whereas triacyl lipopeptide derivatives of *P.gingivalis* lipopolysaccharide plays a vital role in stimulation of cells in a TLR2 dependent manner.³¹ TLR system primarily detects *Porphyromonas gingivalis* through TLR2 rather than TLR4 because the molecule with TLR4 agonistic activity that are expressed by *P.gingivalis* are probably suppressed in the context of the whole organism. The Tetraacylated and dephosphorylated lipid A structure produced by *P.gingivalis* makes the lipopolysaccharide molecule biologically inert and permits the activation of TLR4 and also provides protection against polymyxin B and other cationic antimicrobial peptides. In the diseased sites with increased hemin concentration, there occurs the production of monophosphorylated lipid A which is antagonistic to TLR 4 activation.³¹

Major outer sheath protein of *T.denticola* stimulate TLR2 activity whereas the LPS of the outer sheath activates TLR4 activity resulting in the release of cytokines and nitric oxide. Studies in macrophages, gingival epithelial cells and macrophages have displayed the TLR2 activation of *T.denticola*. The organism may have developed its own way to evade the TLR4 activation of the host defence mechanism by the improper exposure of the LPS on the bacterial cell surface or by possessing a TLR4 antagonistic activity but is indefinite.²⁵ The lipid A component of the LPS of *P.intermedia* stimulates the secretion of interleukin-6 in the murine peritoneal macrophages via TLR4 dependent mechanism but TLR4 is not activated by the whole cells of *P.intermedia*.^{1,3} Purified lipoproteins of *T.forsythia* stimulate TLR2 signalling resulting in the production of interleukin-1, interleukin-8 and TNF α .³

TLRS and Viruses in Periodontitis

TLRs play a vital role in the detection of viruses in the periodontal tissues and Toll like receptor 3, 7, 8 and 9 which are expressed intracellularly detect the viral nucleic acids thereby initiating immune response against the viruses. TLR3 detects the viral nucleic acid. TLR7 and 8 detect the double stranded viral RNA. TLR9 recognises the viral DNA. Binding of TLRs with their respective viral ligands result in the triggering of TLR signalling pathway which in turn result in the stimulation of interferon α and β . TLR4 which is an extracellular TLR can also stimulate the TRAM/TRIF

signalling intracellularly in the endosomes through its relocation.^{1,7}

Single Nucleotide Polymorphisms (SNP) of TLRs

SNP in TLR4 Asp299Gly and Thr399Ile are associated with hyporesponsiveness to LPS and hence are susceptible to gram negative bacterial infections. These mutations are related with severe malaria in African children.²² SNP in TLR2 Arg753Gln was found to be associated with increased susceptibility to tuberculosis in Tunisian population and decreased response to gram positive bacteria especially streptococci. Another polymorphism in TLR2 Arg677Trp has been related to increased susceptibility to lepromatous leprosy in Korean population.²⁰ An increased susceptibility to legionnaires disease is seen in people with the point mutation (392STOP) in TLR5.²⁰ Patients with deficiency of IRAK4 gene are more susceptible to pyogenic gram positive bacteria but also exhibit some resistance to viral, fungal and parasitic infections. SNP in the adaptor MAL (S180L) in people from Kenya, UK and Vietnam is related with a protective effect against infectious diseases like malaria, bacteremia, TB and pneumococcal bacteremia. Contradiction to this study, increased susceptibility is seen to tuberculosis in another MAL polymorphism(c558T).^{20,22}

TLRs in Various Disease Processes

TLRs and the molecules involved in the TLR downstream signalling pathway have been implicated in various disease processes. Initially TLRs were found to detect the pathogen associated molecular patterns (PAMP) on the microbes but later it was observed that TLRs were also involved in the detection of various damage associated molecular patterns (DAMP) which are endogenous ligands and hence may contribute to the pathogenesis of various auto immune, chronic inflammatory and infectious diseases as well as in various cancers.³²

Applications of TLRs

Manipulating the immune response by utilizing TLR agonists or antagonists might be of therapeutic and prophylactic value.¹⁰

TLR Agonists

TLR agonists are similar to PAMPs in function but less toxic but have enhanced pharmacodynamic and pharmacokinetic properties. TLR agonist are more effective when given along with aluminium hydroxide which is the commonly used adjuvant in FDA approved vaccines.¹ Monophosphoryl lipid A (MPLA) is used in infectious diseases and cancers as a prophylactic and therapeutic vaccine. Gaunosine containing compound (loxoribine) and imidazoquinolines (Imiquimod, resiquimod, s-27609) are used in the treatment of papilloma virus induced cutaneous disorders. Short oligodeoxynucleotides (CPG ODN). They can be used as vaccine adjuvants for allergic diseases, cancers (melanoma, lung cancer) and infectious diseases (HBV, HIV, Influenza, Anthrax, etc)¹⁰

TLR Antagonists

These are structural ligands that binds to TLR but do not induce signal transduction and hence the release of inflammatory mediators are prevented. Eritoran and Resatorid are used in septic shock. DV1079 and CPG 52364 in the

treatment of auto immune disorders such as SLE, psoriasis, rheumatoid arthritis, etc.

TLRs in Periodontal Vaccines

TLR agonists are potential agents that bridge the innate and adaptive immunity and hence function as vaccine adjuvant to improve the immune response against the co-inoculated antigens.³³ TLRs can influence the naive T-cell response in periodontitis. The T-cell response in periodontal disease is not clear regarding which is protective and which is destructive. There is supportive evidence that the T helper cells predominate the early periodontal lesions and when this cannot be sustained may result in the T helper 2 mediated disease progression but it lacks conclusive evidence. In contrast, some other studies have implicated the destructive effects of Th 1 cells. TLR detects both microbial and non microbial ligands and hence selection of vaccine adjuvants and precise targeting is difficult and is also very crucial because the incorrect choice of adjuvants can result in deleterious effects.³⁴

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