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Toll like receptors in periodontal health and disease

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Abstract
A bacterial infection that affects the periodontium in various ways is called periodontitis. Bacterial plaque triggers the inflammatory response in the host, which damages the host's tissue. In response to microbial invasion, it is now understood that the immune system uses a family of pattern-recognition receptors termed Toll-like receptors as a mechanism to initiate an inflammatory response. TLRs, or toll-like receptors, were first identified in the drosophila and released antimicrobial compounds to fight fungus. The primary sensors of the innate immune response are toll-like receptors. Understanding how toll-like receptors contribute to gingivitis and periodontitis aids in the treatment of periodontal disease using the host modulation therapy approach.

Keywords: Toll like receptors (TLRs), innate immunity, self-tolerance, key sensors.

Introduction
Heat, chemical agents, or bacterial infection are just a few of the injuries or insults that can cause inflammation, which is the body's natural response. The immune system employs a number of strong effector mechanisms that are capable of eliminating a variety of poisonous and allergenic substances as well as a variety of microbial cells. Mammals' immune systems distinguish between self and non-self in order to find and destroy invasive harmful germs. The two branches of this immune system are "innate immunity" and "adaptive immunity." Self-tolerance is the immune system's capacity to protect self-tissues from harm. This process has been thoroughly researched since it lies at the core of the vast class of autoimmune disorders. It is now known that numerous components of both the innate and adaptive immune responses exhibit mechanisms to prevent reactivity against self-antigens. The response is quick and only lasts a short time during the acute phase of inflammation. The response might be thought of as non-physiologic or pathologic if the trauma or injury is not healed. The adaptive immune response is triggered when inflammation progresses into chronicity, involving both cellular and noncellular mechanisms of acquired immunity [1].
Invertebrates' initial line of defence against encroaching microbes is the innate immune response. Phagocytes such dendritic cells, macrophages, and neutrophils are the primary players in innate immunity. In mammals, the TLRs serve as the primary sensors of microbial infection. Through a sophisticated network of signalling, TLRs, which serve as the primary sensors for innate immunity, control the activation of hundreds of host genes to enable an appropriate response to a specific microbial pathogen [2]. An ongoing bacterial infection called periodontitis damages the bone that supports the teeth as well as the gingiva. Bacterial plaque causes tissue damage by inducing an inflammatory reaction in the host. In response to microbial invasion, it is now understood that the immune system uses a family of pattern-recognition receptors termed Toll-like receptors as a mechanism to initiate an inflammatory response [3].

TLR evolution and history
Toll gene products were identified as being essential for the embryonic development of dorsal-ventral polarity in the fruit fly, Drosophila, in 1985. Additionally, the Toll protein, which can be bound to to trigger the release of antimicrobial proteins, mediates the immunological response to a fungal infection in Drosophila.

In 1991, it was discovered that the interleukin 1-receptor and the Toll protein's cytoplasmic domains shared a similar sequence, supporting their participation in the immunological response. The Toll-IL-I receptor domain is the name of this cytoplasmic region. Later, mammalian homologues of the Drosophila Toll, known as Toll-like receptors, were discovered [4].

TLRs are the end result of a process of evolution that started before plants and animals split apart. They may be recognised by a highly conserved intracellular Toll interleukin (IL)-1 receptor (TIR) motif. Plant disease resistance genes that code for TIR-bearing proteins reflect homologues of these proteins in plants, albeit their exact methods of action are still understood. Toll, the first member of the TLR family in insects, most notably Drosophila, was demonstrated to be in charge of the adult fly's anti-fungal responses in 1996. (Lemaitre B 1996). Using naturally occurring mouse strains that respond poorly to endotoxin, this discovery led to the identification of a mammalian TLR (Medzhitov R 1997), and a vital relationship to immune function was established. Careful genetic research revealed mutations in the gene encoding TLR4. More than thirteen TLRs have been identified in humans and mice to yet [5].

In Mammals TLR'S

There are currently 10 members of the TLR family, and more will undoubtedly be discovered in the future. Each human TLR gene's chromosomal location has been identified. According to a comparison of the amino acid sequences of human TLRs, there are five subfamilies that make up the TLR family: TLR3, TLR4, TLR5, TLR2, and TLR9. TLR1, TLR2, TLR6, TLR10, and TLR2 are members of the TLR2 subfamily. TLR7, TLR8, and TLR9 are members of the TLR9 subfamily. TLR1 and TLR6 belong to the TLR2 subfamily and share 69.3% of their amino acid sequence overall. However, both receptors' TLR domains are extremely conserved, showing around 90% identity (figure 1) [6].

Why Are TLRs Necessary?

Since a very long time, it has been understood that certain non-antigenic microbial components, such as LPS and mycobacterial substances in complete Freund's adjuvant (CFA), may cause immunological reactions. The molecular processes underlying these roles are still unknown, though. There are currently many known uses for TLRs and their specific ligands, whether by gene knockdown methods or other methods. Immune sensors known as TLRs, which are extensively expressed on immune cells, recognise specific chemicals known as pathogen-associated molecular patterns (PAMPs) presented by microbial components to elicit immunity. They all have a role in the beginning and activation of immunity, despite having different ligand specificities, expression patterns, and signalling routes [7]. PAMPs: PAMPs for Pathogen-Associated Molecular Patterns

A wide variety of diseases all have microbial compounds that cause the innate immune system to react strongly. These pathogen-associated molecular patterns are different from those observed in the host and are typically repetitive in nature. Additionally, pathogen-associated molecular patterns are necessary for the organism's survival and pathogenicity but are not prone to antigenic change. Microbial carbohydrates, which are a typical structure that many species of bacteria use to decorate their cell walls, are an excellent illustration of this. Additionally typical among microbial compounds are lipid alterations. It is believed that pattern recognition receptors, including Toll-like receptors, are drawn to pathogen-associated molecular patterns (figure 2 & table 1) [8].

TLR Structure

TLRs belong to a wider superfamily of interleukin-1 receptors; there are several different extracellular sections. TLRs have a leucine-rich repeat (LRR) pattern in their extracellular region, whereas IL-1Rs have three immunoglobulin domains. The LRR domains are made up of repeats that range in number and are each 24-29 amino acids long. They contain the motif XXLXLXX as well as additional conserved leucines. These LRR domains are believed to play a direct role in the identification of many infections.

IL-1Rs that exhibit a considerable amount of cytoplasmic homology. The Toll/IL-1R (TIR) domain, a conserved area of 200 amino acids in the cytoplasm of TLRs and members of the IL-1R family, is particularly important. The three conserved boxes (1, 2 and 3) that contain amino acids essential for signalling make up the TIR motif's homology area. A number of adaptor proteins that also possess TIR domains interact with the TIR domain of the TLR. The kinase family known as the IL-1R-associated kinases (IRAKs) is recruited by the universal adaptor protein MyD88, which ultimately leads to the activation of NF-kB and the generation of proinflammatory cytokines. The immune defence of people and other mammalian species depends on understanding the underlying molecular specifics of this signalling pathway (figure 3) [9].

Disbursement of TLRs

Different subsets of dendritic cells express different TLRs. Myeloid dendritic cell (MDC) and plasmacytoid dendritic cell are two subgroups of dendritic cells seen in human blood (PDC). While PDCs only express TLR7 and TLR9 and MDCs only express TLR1, 2, 4, 5, and 8, there have been some reports suggesting TLR7 is also expressed in MDC. When exposed to microbial components, immature dendritic cells develop into mature ones, and as they do, different TLRs express themselves in distinct ways. TLR 1, 2, 4, and 5 expression is present in developing dendritic cells but declines with maturation. Only mature dendritic cells express TLR3. TLR expression varies according to dendritic cell subsets and phases of maturation [10].

Regulation TLR Expression

TLR's expressed through analyses of TLR-mediated signalling pathways

A MyD88-dependent pathway is comparable to signalling pathways through the IL-1 receptors. It is a signalling pathway dependent on myd88. MyD88 connects with the TIR domain of TLRs due to the presence of a C-terminal TIR domain and an N-terminal death domain. Through interaction of the death domains of both molecules during activation, MyD88 attracts IRAK-4 to TLRs and enhances IRAK-4-mediated phosphorylation of IRAK-1**.** When IRAK-1 is then associated with TRAF6, two different signalling pathways are activated. Through one mechanism, MAP kinases are activated, which then activates AP-1 transcription factors. The TAK1/TAB complex is activated through a different route, which increases the activity of the IKK complex (IkB kinase). Once active, the IKK complex causes IkB to be phosphorylated and then degraded, which causes NF-kB to be translocated into the nucleus. As implied by its name, MyD88 is an essential component of the MyD88-dependent pathway.

Inflammatory cytokines including TNF- and IL-12p40 are not produced by MyD88-deficient mice in response to any TLR ligand. Thus, all TLRs require MyD88 for the generation of inflammatory cytokines (figure 4).

TRIF-dependent pathway for MYD88

TLR4 ligand-induced generation of inflammatory cytokines is not seen in MyD88-deficient macrophages, while NF-kB activation is seen with delayed kinetics. This shows that there is a MyD88-independent component in TLR4 signalling even though TLR4-mediated generation of inflammatory cytokines totally depends on the MyD88-dependent pathway. The transcription factor IRF-3 and the late phase of NF-kB activation are both activated by TLR4 stimulation in a way that is MyD88-independent, according to later research. IRF-3 is activated by TLR4 and produces IFN-b as a result. Stat1 is activated by IFN-b, which in turn triggers many IFN-inducible genes. IRF-3 is activated by viral infection or dsRNA, it was discovered. As a result, the TLR3-mediated pathway also activates IRF-3 and causes IFN-b in a way that is independent of MyD88 (figure 5). So, in order to trigger IFN-b12, TLR3 and TLR4 use the MyD88-independent component. Other adaptors, including those in the Myd88-independent pathway, were discovered after a database search for molecules with structural similarities to the myeloid differentiation primary response protein 88:

- Toll–IL-1 receptor domain-containing adaptor protein/Myeloid differentiation primary response protein 88 – adaptor-like (TIRAP/MAL)
- Toll-IL-1 receptor domain-containing adaptor inducing interferon-β (TRIF)
- TRIF-related adaptor molecules (TRAM) [13].

TLR Regulation In A Bad Way

Biological elements that stimulate TLRs cause the production of inflammatory cytokines such TNF-a, IL-6, and IL-12. All of these cytokines cause major systemic diseases with a high mortality risk in the patient when they are produced in excess. It follows that the development of methods by which organisms can control their TLR-mediated responses is not surprising. When exposed to microbial components like LPS, the body's ability to respond to a later LPS challenge is much diminished. Endotoxin (or LPS) tolerance has been used to refer to this phenomena since it was originally observed more than 50 years ago, but the exact processes are still unknown. Several models are put out since the mechanisms are currently being examined in the context of TLR signalling. Reduced surface expression of the TLR4 and MD-2 LPS receptor complex, a cofactor that promotes LPS binding, is observed in macrophages stimulated with LPS. Reduced expression of IRAK1 is induced by TLR2, TLR7, and TLR4 ligands. It has also been demonstrated that additional mechanisms contribute to LPS tolerance. Additionally, compounds that inhibit TLR signalling have been discovered. Induced by TLR stimulation in monocyte/macrophages, IRAK-M, a member of the IRAK family of serine/threonine kinases, lacks kinase activity. In response to TLR ligands, inflammatory cytokines are produced more often in IRAK-M-deficient animals, and LPS tolerance is improperly induced IRAK-inhibitory M's activity appears to be caused by its ability to stop IRAK-1/IRAK-4 from dissociating from MyD88, which prevents the formation of the IRAK-1-TRAF6 complex (figure 6).

Monocytes stimulated with LPS produce MyD88s, an alternatively spliced form of MyD88 lacking the intermediary domain of MyD88. When MyD88s are overexpressed, IRAK 4-mediated IRAK-1 phosphorylation is inhibited, which reduces LPS-induced NF-kB activation.

The SOCS family of proteins, which are activated by cytokines and control cytokine signalling pathways, includes SOCS1. In addition to cytokines, SOCS1 expression in macrophages was increased by TLR ligands like LPS and CpG DNA. Mice lacking SOCS1 had increased sensitivity to endotoxin shock brought on by LPS and had poor LPS tolerance induction. When SOCS1 was expressed erratically, LPS-induced NF-kB activation in macrophages was compromised. These results suggest that SOCS1 directly suppresses TLR signalling pathways, however the exact mechanism by which SOCS1 does this is still unknown. It has also been demonstrated that membrane-bound proteins with the TIR domain, such as T1/ST2 and SIGIRR (single immunoglobulin IL-1 receptor-related molecule), participate in the inhibition of TLR signalling. The LPS-induced inflammatory response was boosted in animals lacking SIGIRR and T1/ST2.

In both resident and non-resident cells involved in the pathogenesis of disease progression, biologic mediators are removed by PAMPS (figure 7 & Table 2)

Pathobiology of progression of periodontal disease:

The pathogenic processes of periodontal diseases are mostly the outcome of the host's reaction to tissue loss brought on by microbial infection. As was previously said, bacteria, particularly LPS, start these harmful processes, but the host then spreads them. In order to provide nutrients for their growth" for subsequent tissue invasion, periodontal pathogens produce toxic compounds and enzymes (such as hyaluronidascs, collagenases, and proteases) that dissolve extracellular matrices like collagen and even host cell membranes. Key virulence factors generated by P. gingivitis include arg- and lys-gingipain cysteine proteinases, which are thought to be necessary for considerable tissue component breakdown and host tissue invasion. Many of the surface protein molecules produced by microbes have the ability to stimulate the host's immune system and cause local tissue inflammation. P. gingivalis has a variety of virulence factors on its cell surface, including cytoplasmic membranes, peptidoglycans (PGNs), outer membrane proteins, LPS, capsules, and fimbriae. All of these virulence factors are capable of triggering the host's defence mechanism.

Leukocytes and fibroblasts, or structural cells of the tissues, release a variety of inflammatory chemicals, such as proteases, MMPs, cytokines, prostaglandins, and host enzymes, once the immunological and inflammatory processes have begun. The collagen structure of the tissues is typically broken down by proteases, which opens up pathways for further leukocyte infiltration. In mature connective tissues of vertebrates, the cross-links hydroxylysylpyridmuline (HP) and its deoxy analogue, lysylpyridinoline (LP), also known as pyridinoline (Pyr) and deoxypyridinoline, respectively, are widely distributed. However, LP, despite being widely distributed, is most prominent in bone and dentin. The pyridinoline residues left behind after collagenase digestion can be employed as indicators, and both HP and LP are enhanced in tissue with greater collagen resorption [14].

The destruction of the collagen fibres and connective tissue connection to the tooth, the proliferation of epithelial cells apically along the root surface, and the deepening of periodontal pockets are all symptoms of periodontal disease. The amount of the tissue's inflammatory infiltration increases

together with the junctional epithelium's migration apically. Additionally, active osteoclasts start breaking down bone [15].

Toll gates to vaccine treatment and periodontal host modulation [16].

Given the variety and significance of the roles that toll-like receptors perform, it is possible that therapeutic modification of toll-like receptor signalling will have an impact on infection control, inflammation attenuation, and the creation of periodontitis vaccine adjuvants. In order to successfully apply toll-like receptor-based treatment methods in periodontitis, intervention must be extremely selective and carefully targeted. Toll-like receptor signalling pathways in response to periodontal infections would then need to be precisely characterized, and efficient and targeted agonists or antagonists of toll-like receptor activity and signalling would also need to be developed.

Overview of recent periodontitis host modification treatments: Although frequently ineffective on their own, mechanical methods like scaling and root planning to lower the quantity of periodontal bacteria are crucial for periodontal therapy [17, 18].

Thus, a number of adjuvant therapy for host response regulation have been suggested and evaluated in either clinical or experimental settings. When it was discovered that sub antimicrobial doses of this medication suppressed the activity of matrix metalloproteinases, tetracyclines attracted a lot of attention [19]. Under pathological circumstances, matrix metalloproteinases are more prevalent and have a role in the degradation of periodontal tissues, in part through activating toll-like receptors [20]. Doxycycline, the most effective tetracycline in inhibiting collagenolytic activity, has been proven to be generally advantageous as a supplement to scale and root planning in the treatment of periodontitis patients. In comparison to scaling and root planning plus a placebo, scaling and root planning plus doxycycline is particularly successful in terms of clinical attachment gain, reduction in probing depths, and reduction in gingival crevicular fluid levels of certain matrix metalloproteinases [21]. The dose and frequency of doxycycline treatment have been changed in an effort to increase the therapeutic benefits of the combined scaling and root planning method [22]. If combined with other, compatible therapeutic drugs that have not yet been discovered, it is possible that this treatment could have even more protective effects.

Nonsteroidal anti-inflammatory medicines can be administered systemically or topically as another method of controlling the host response in periodontitis [23]. The ability of nonsteroidal anti-inflammatory medications to suppress the activity of both cyclooxygenase isoforms makes them either nonselective or selective (i.e. cyclooxygenase-1 and cyclooxygenase-2, or only cyclooxygenase-2, respectively). The inducible isoform prevalent in inflammatory cells is represented by cyclooxygenase-2. Arachidonic acid is the substrate used by both cyclooxygenases 1 and 2 to create prostanoids, of which prostaglandin E2 is closely linked to the deterioration of periodontal tissue [25]. Nonselective nonsteroidal anti-inflammatory medications have been reported to limit alveolar bone resorption in studies in animal models and human trials, albeit typically unsatisfactory results were seen in their ability to effect clinical attachment gains or decreases in probing depth [26]. More recently, it was demonstrated that using specific cyclooxygenase-2 inhibitors prevented rats' loss of periodontal bone [27]. Treatment with selective cyclooxygenase-2 inhibitors may help patients avoid some of the side effects of nonselective, nonsteroidal anti-inflammatory medication use, including kidney toxicity and damage to the gastrointestinal mucosa. The reversal of the cyclooxygenase-2-dependent reduction of tissue factor production, a protein that promotes blood clotting, can result in prothrombotic side-effects, hence cyclooxygenase-2 inhibitors are not without risk either. Topical administration of nonsteroidal anti-inflammatory medications may help to lower the risk of systemic adverse effects because some nonsteroidal anti-inflammatory medications (such as flurbiprofen) are easily absorbed by the gingiva.

Inflammation resolution is now understood to be an active process mediated by certain proresolution agonists of endogenous (host) origin. Small lipid molecules like lipoxins and resolving, which are produced from arachidonic acid and other polyunsaturated fatty acids, respectively, and are being evaluated for the treatment of disorders that are characterised by inflammation, including periodontitis, are examples of such agonists [28]. In transgenic rabbits, a proof-of-concept investigation on the effectiveness of lipoxin A4 at preventing P. gingivalis-induced periodontitis was carried out [29]. These animals have elevated levels of lipoxin A4 due to overexpression of 15-lipoxygenase. In comparison to nontransgenic control rabbits, 15-lipoxygenase transgenic rabbits showed considerably less periodontal bone loss and gingival inflammation after oral infection with P. gingivalis. 53 Furthermore, in normal (i.e. nontransgenic) rabbits, topical administration of a stable analogue of lipoxin A4 prevented experimental periodontitis caused by P. gingivalis. Resolvin E1 was applied topically, and similar protective benefits in the same experimental model were detected. The ability of lipoxin A4 and resolvin E1 to prevent excessive neutrophil recruitment (and hence reduce neutrophil-mediated periodontal tissue damage) and to facilitate the resolution of inflammation was attributed to their protective properties. Compared to nonsteroidal anti-inflammatory medications, which may actually hinder the resolution of inflammation, proresolving agents may have advantages. Although cyclooxygenase-2 plays a pro-inflammatory role in the early stages of neutrophil-dominated inflammation (e.g., via prostaglandin E2), it also aids in the resolution of inflammation during a later, mononuclear cell-dominated phase by producing pro-resolving prostaglandins (e.g., prostaglandin D2). Nonsteroidal anti-inflammatory medications may thereby negate the advantages of proresolving prostaglandins. Proresolution agonists are believed to mimic how inflammation resolves physiologically, in contrast to traditional anti-inflammatory treatments, which may also interfere with defensive mechanisms against infection, especially when systemically delivered. Timing appears to be crucial since there is a risk of prematurely resolving an inflammatory response before it has had an opportunity to control infection with the exogenous use of proresolving drugs in infection-driven inflammatory disorders. Additionally, resolvins (at least those of the D series) prevent macrophage activation that is mediated by the toll-like receptor-4, which may have a negative impact on the body's natural defences. However, it is possible that these potential problems could be at least partially eliminated by the development of antimicrobial actions by certain proresolution molecules [25].

The pharmacological class known as "bisphosphonates" has been used to treat and prevent osteoporosis because it inhibits bone resorption and osteoclast activity. 55 Several research were carried out in periodontitis animal models to investigate their potential therapeutic utility in the condition. These

investigations demonstrated that bisphosphonates can prevent alveolar bone loss without simultaneously reducing gingival inflammation. When bisphosphonates (alendronate or risedronate) were used in conjunction with scaling and root planing for periodontitis patients, similar protective effects (reduced alveolar bone loss and enhanced mineral density) were seen. Regarding their impact on various clinical indicators, such as clinical attachment level, probing pocket depth, and gingival index, mixed results were found. Therefore, it can be said that bisphosphonates can at least prevent bone loss. Given the new discovery that bisphosphonates may be linked to osteonecrosis of the jaws, more long-term trials may be required to demonstrate safety..

At least in part, the actions of bisphosphonates on key molecules involved in the control of osteoclast function could be used to explain why these drugs have an inhibitory effect on bone resorption. In particular, a trio of proteins from the tumour necrosis factor/tumor necrosis factor-receptor family—the receptor activator of nuclear factor-kB ligand (RANKL), receptor activator of nuclear factor-kB (RANK), and its decoy receptor osteoprotegerin—play a crucial role in osteoclast recruitment, differentiation, and activation. By preventing the binding of RANKL, which is expressed by osteoblasts, fibroblasts, T cells, and B cells, to RANK on osteoclast precursors, osteoprotegerin performs a regulatory function. By primarily raising osteoprotegerin levels, bisphosphonates appear to lower the RANKL to osteoprotegerin ratio. Additionally, the RANKL-RANK-Osteoprotegerin axis has been specifically addressed for the therapy of osteolytic diseases. Although RANKL-mediated osteoclastogenesis may not be solely to blame for the production of bone loss in periodontal systems or in other experimental systems, this may be a significant therapeutic strategy for decreasing inflammatory bone loss in periodontitis. In fact, in proof-of-concept studies, systemic or local application of osteoprotegerin (a fusion protein with the immunoglobulin Fc domain) to mice or rats reduced the induction of experimental periodontal bone loss. A recent clinical investigation, which is significant, shown that the RANKL/osteoprotegerin ratio is dramatically increased in periodontitis and that it is favourably connected with clinical attachment degree and probing pocket depth. Another study that supports this conclusion discovered a strong correlation between gingival expression of RANKL but not osteoprotegerin and elevated P. gingivalis levels. These clinical findings give osteoprotegerin's usage as a RANKL antagonist yet another justification.

However, the recent discovery from clinical trials that osteoprotegerin- Fc treatment results in elicitation of auto-antibodies, which impede its biological activity, poses a possible problem with the use of osteoprotegerin- Fc as a therapeutic agent. Denosumab, also known as AMG 162, is a humanised anti-RANKL monoclonal antibody that was developed to treat osteoporosis. It appears to solve these drawbacks. The only currently approved bone-resorption inhibitors, bisphosphonates, may not be as effective as RANKL inhibitors. Blocking the RANK-RANKL relationship, however, might also alter how bones are metabolised as well as how well the immune system works normally. In this sense, RANKL boosts macrophage and dendritic cell activity, survival, and antigen-presenting activity, demanding further research into the safety of RANKL inhibitors. Additionally, the inability of RANKL antagonistic methods to cure synovitis in rheumatoid arthritis is a drawback. Comparatively speaking, RANKL suppression in periodontitis may prevent bone resorption but is unlikely to reduce inflammation or stop the infection. Anti-RANKL medication may therefore need to be used in conjunction with other therapeutic techniques in cases of human periodontitis. 29

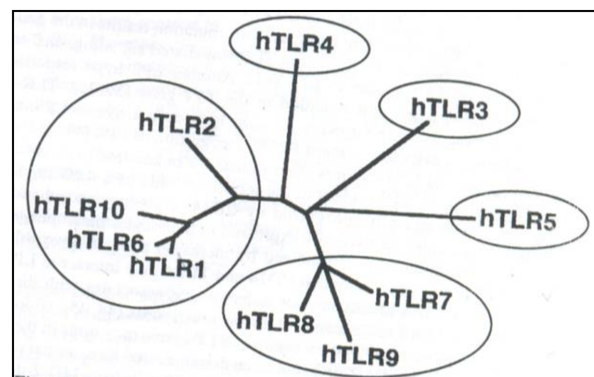

Fig 1: Phylogenetic tree of human Toll-like receptors (TLRs).

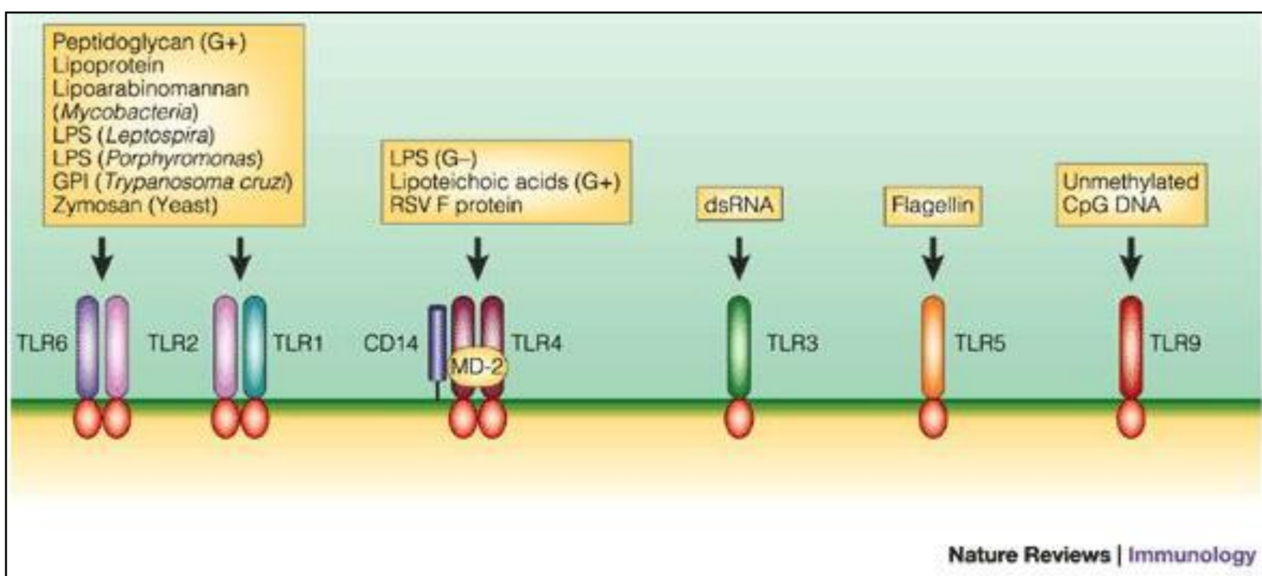

Fig 2: Ligend specificities of TLRs.

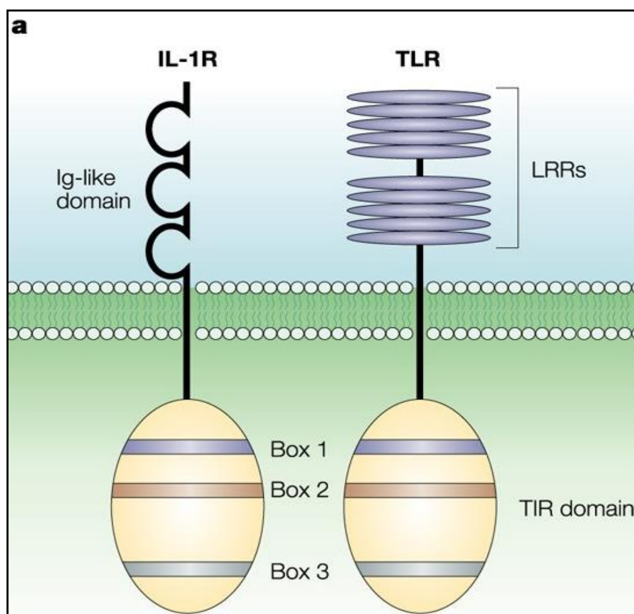

Fig 3: Structure of TLR

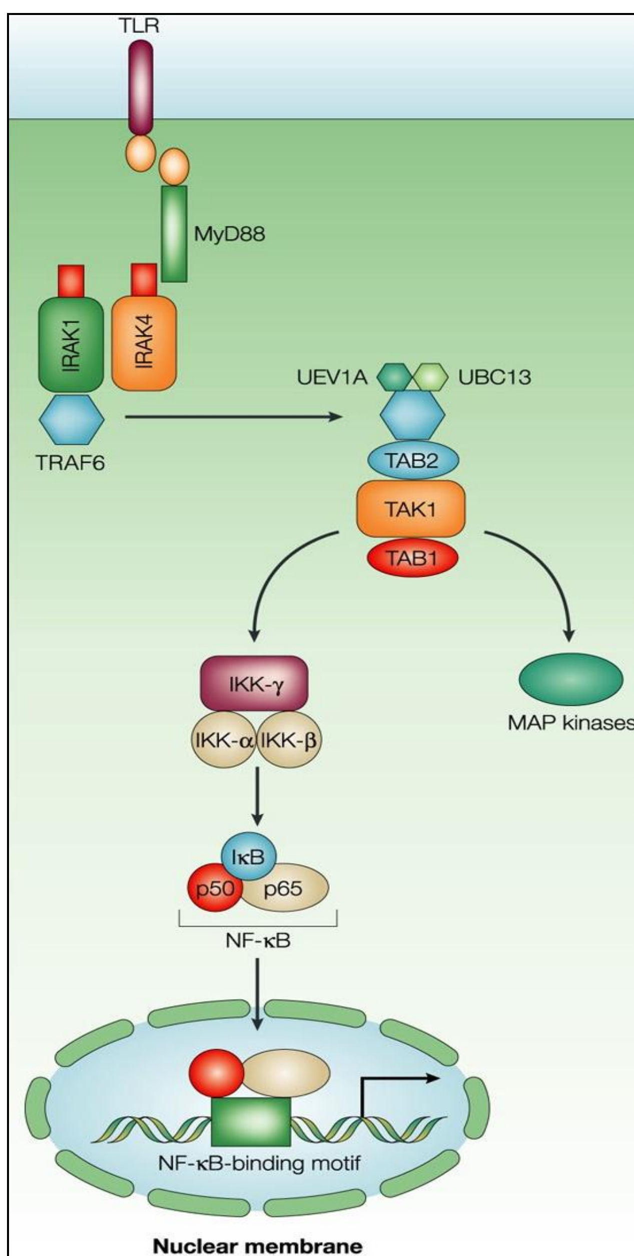

Fig 4: Myd88 – Dependent Signaling Pathwa

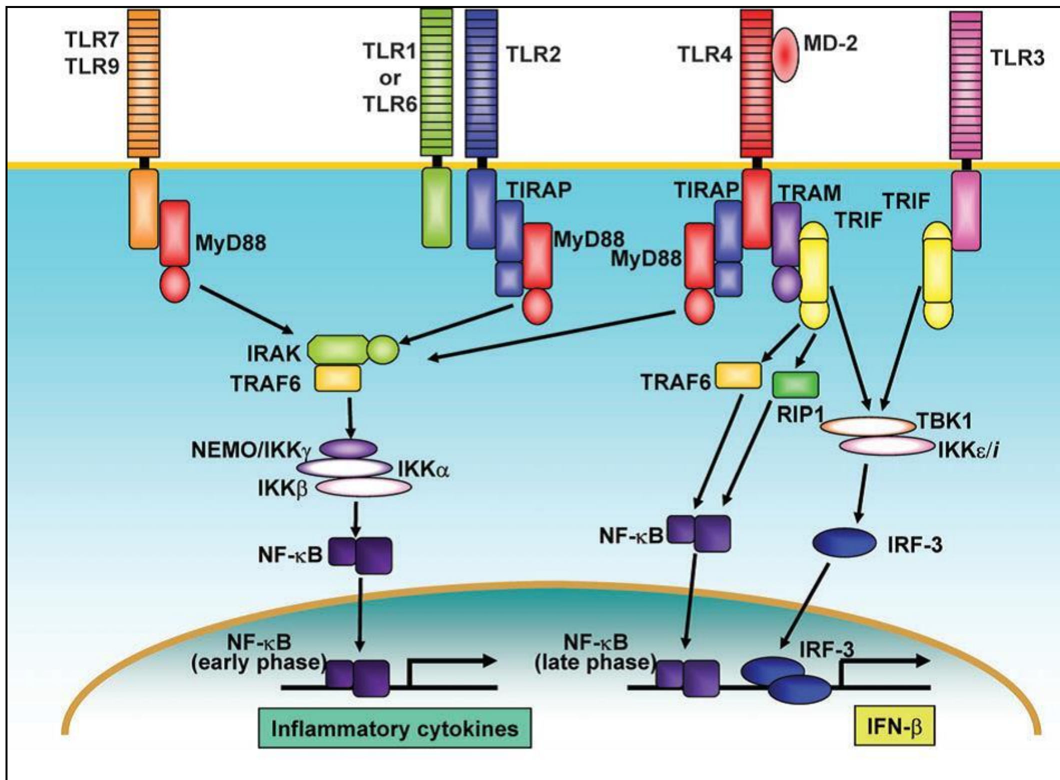

Fig 5: MyD88 dependent and independent pathway

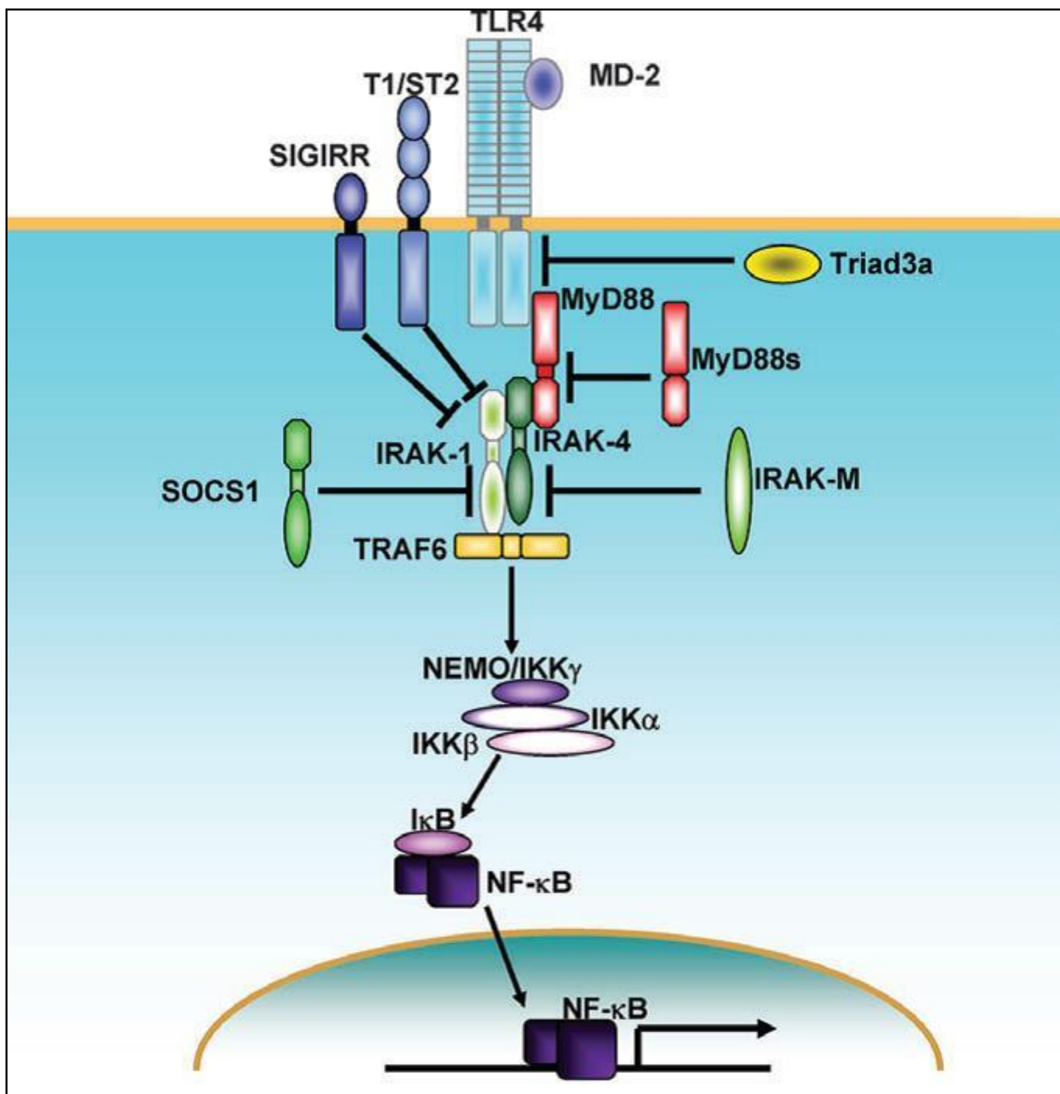

Fig 6: Negative regulation of tlr signaling

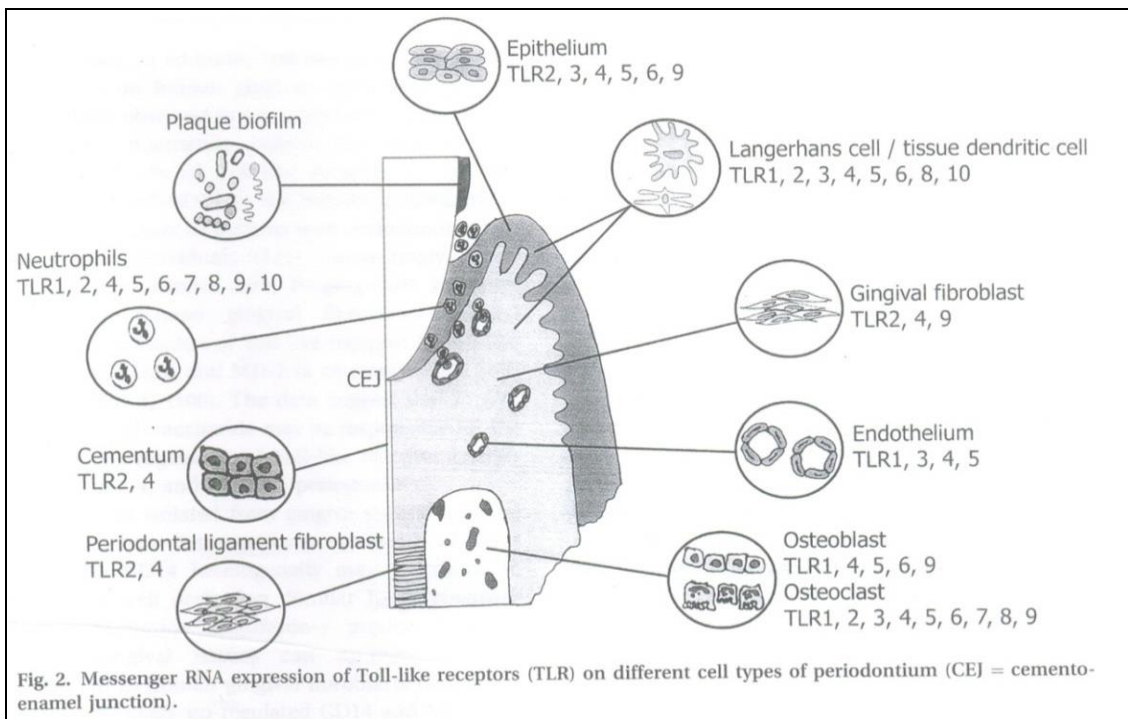

Fig 7: Messenger RNA expressions of TLRs on different cell types of periodontium are represented in this picture.

Table 1: Toll Like Receptors And Their Ligands

TLR'S	Ligands
TLR1	Tri-acyl lipopeptides (bacteria, mycobacteria); Soluble factors (Neisseria meningitidis); Modulin
TLR2	Lipoprotein/lipopeptides; Peptidoglycan (Gram-positive bacteria) ; Lipoteichoic acid (Gram-positive bacteria); Lipoarabinomannan (mycobacteria); Glycoinositolphospholipids (Trypanosoma Cruzi); Glycolipids (Treponema maltophilum); Porins (Neisseria); Zymosan (fungi); Listeria (Heat-killed bacteria); LPS (Spirochaetae); Modulin
TLR3	DsRNA
TLR4	LPS (Gram-negative bacteria); HSP60 (Chlamydia pneumoniae); HSP60 (host); HSP70 (host); Fusion protein (RSV); Taxol (Plant); Envelope proteins (MMTV)
TLR5	Bacterial flagellin
TLR6	Di-acyl lipopeptides (mycoplasma); Modulin; soluble tuberculosis factor (STF)
TLR7	GU rich Single-strand RNA (ssRNA), Imidazoquinoline (synthetic compounds); Loxoribine (synthetic compounds); Bropirimine (synthetic compounds)
TLR8	GU rich Single-strand RNA (ssRNA)
TLR9	CpG-containing DNA (viral and bacterial)
TLR10	Unknown
TLR11	Toxoplasma profilin
TLR12 and TLR13	Unknown

Table 2: Biologic Mediators Elicted By PAMPS In Resident And Non Resident Cells Involving In The Pathogenesis Of The Disease Progression

Cell type	PAMPs	Biologic mediators
Epithelial cells	LPS, fimbriae, glycoprotein, whole bacteria, cell wall extracts	IL-8, G-CSF, GM-CSF, β-defensin-2, MMP-3, MMP-9
Dendritic cells	Fimbriae, LPS, CpGDNA, DNA	IFN-α, IL-6, IL-8, IL-10, IL-12, TNF-α, GM-CSF
Endothelial cells	LPS, Heat-shock proteins	IL-6, GM-CSF, ICAM-1
Gingival fibroblasts	LPS, Peptidoglycan, CpGDNA	IL-1β, IL-6, IL-8, TNF α, PGE_2 MCP-1
PDL fibroblasts	LPS	IL-6, IL-8, MMP-13
Cement oblasts	LPS	OPN, OCN, RANKL
Macrophages	LPS, CpGDNA	IL-1α, IL-1β, IL-6, IL-12, TNF-α, MMP-1, NO
Osteoblasts	LPS	IL-1β, IL-6, TNF-α, RANKL, MMP-2, MMP-9, NO, PGE_2
Neutrophils	DNA	IL-8, Chemotaxis, shedding of L-selectin
Monocytes	LPS, CpGDNA, fimbria	IFN-γ, IL-1β, IL-6, IL-8, IL-12, TNF-α, RANKL, PGE_2
B-lymphocytes	CpGDNA, Heat stress proteins, cell sonicate extracts	IL-6, IL-10, IL-12, TNF-α, proliferation, antibody production
T-lymphocytes	LPS, CpGDNA, peptidoglycan	IFN-β, IL-4, IL-10, IL-13, inhibition of apoptosis

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