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Review Article

# Sensing and signaling in periodontal inflammation via toll like receptors: A review

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ABSTRACT

Periodontal disease is a chronic inflammatory condition that affects the supporting structures of teeth, including the gingiva, periodontal ligament, and alveolar bone. Toll-like receptors (TLRs) play a crucial role in the recognition of pathogen-associated molecular patterns (PAMPs) from bacteria that cause periodontal disease. TLR activation triggers an inflammatory response that aims to eliminate the bacteria and repair damaged tissue. However, if the inflammation persists, it can lead to further tissue destruction and bone loss. This review discusses the mechanisms of TLRs in periodontal disease progression, including the recognition of bacteria, activation of immune cells, tissue destruction, and inhibition of immune response. Strategies for down-regulating TLRs, such as small-molecule inhibitors, antibodies, natural products, micro RNA, and nutritional interventions, are also discussed. Targeting TLRs is a promising therapeutic approach for reducing chronic inflammation associated with periodontal disease. Further research is needed to develop safe and effective strategies for down-regulating TLRs in humans.



## 1. Introduction

Toll-like receptors (TLRs) are a type of protein receptor that play a key role in the innate immune system. They are found on the surface of cells that are involved in the immune response, such as macrophages, dendritic cells, and B cells. TLRs are able to recognize specific molecular patterns that are associated with different types of pathogens, such as bacteria, viruses, and fungi. When a TLR binds to a pathogen-associated molecular pattern (PAMP), it triggers a signaling pathway that leads to the activation of the immune response.[1]

There are 10 different types of TLRs in humans, each of which recognizes a specific type of PAMP. For example, TLR4 recognizes lipopolysaccharides (LPS) found on the surface of gram-negative bacteria, while TLR7 recognizes single-stranded RNA found in viruses.[2]

TLRs are also involved in recognizing and responding to damaged or stressed cells, as well as in the development of autoimmune disorders. Therefore, understanding the role of TLRs in the immune system is important for the development of new therapies and vaccines for infectious and autoimmune diseases.

### *1.1. Toll like receptors in periodontitis*

Periodontitis is a chronic inflammatory disease that affects the tissues that support teeth, including the gums, periodontal ligament, and alveolar bone. Toll-like receptors (TLRs) have been shown to play an important role in the

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immune response to periodontitis.[3]

The bacteria associated with periodontitis are recognized by TLRs on immune cells, which triggers an inflammatory response. This response is intended to eliminate the bacteria and repair the damaged tissue, but if it becomes chronic, it can lead to further tissue destruction and bone loss.[4]

Studies have shown that several TLRs are involved in the immune response to periodontitis, including TLR2, TLR4, and TLR9. TLR2 recognizes bacterial lipoproteins and peptidoglycans, while TLR4 recognizes lipopolysaccharides (LPS) found on the surface of gram-negative bacteria. TLR9 recognizes bacterial DNA.[5]

Research has also shown that the expression of TLRs is increased in the inflamed tissues of individuals with periodontitis, indicating a heightened immune response. Additionally, genetic variations in TLR genes have been associated with an increased risk of developing periodontitis.

Targeting TLRs has been proposed as a potential therapeutic approach for treating periodontitis. However, more research is needed to better understand the role of TLRs in periodontitis and how they can be targeted for therapeutic benefit.

### *1.2. Types of toll like receptors*

There are 10 different types of Toll-like receptors (TLRs) identified in humans. Each TLR recognizes different pathogen-associated molecular patterns (PAMPs) and activates distinct signaling pathways to induce an immune response. The 10 different types of TLRs are:

1. TLR1: recognizes triacyl lipopeptides and is involved in the recognition of bacterial and fungal cell wall components.
2. TLR2: recognizes diacyl and triacyl lipopeptides, peptidoglycans, lipoteichoic acids, zymosan, and lipoarabinomannans, and is involved in the recognition of bacterial, fungal, and mycobacterial cell wall components.
3. TLR3: recognizes double-stranded RNA and is involved in the recognition of viral infections
4. TLR4: recognizes lipopolysaccharides (LPS) found on the surface of gram-negative bacteria, and is involved in the recognition of bacterial infections.
5. TLR5: recognizes flagellin and is involved in the recognition of bacterial infections
6. TLR6: recognizes diacyl lipopeptides and is involved in the recognition of bacterial and fungal cell wall components.
7. TLR7: recognizes single-stranded RNA and is involved in the recognition of viral infections
8. TLR8: recognizes single-stranded RNA and is involved in the recognition of viral infections
9. TLR9: recognizes unmethylated CpG motifs found in bacterial DNA and is involved in the recognition of bacterial infections.
10. TLR10: recognizes lipopeptides and is involved in the recognition of bacterial and fungal cell wall components.

TLRs are expressed on various immune cells, including macrophages, dendritic cells, and B cells, and play a critical role in the innate immune response by detecting and responding to invading pathogens.[6]

### *1.3. Mechanism of toll like receptors in periodontal disease progression*

Toll-like receptors (TLRs) are involved in the recognition of pathogen-associated molecular patterns (PAMPs) from bacteria that cause periodontal disease. The activation of TLRs on immune cells triggers an inflammatory response, which is intended to eliminate the bacteria and repair the damaged tissue. However, if the inflammation becomes chronic, it can lead to further tissue destruction and bone loss.[7]

The mechanism of TLRs in periodontal disease progression involves the following steps:

1. Recognition of bacteria: TLRs on immune cells recognize PAMPs on the surface of bacteria, such as lipopolysaccharides (LPS) and peptidoglycans, leading to their activation.
2. Activation of immune cells: The activation of TLRs on immune cells triggers a signaling cascade, leading to the production of proinflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-$\alpha$), and the recruitment of immune cells to the site of infection.
3. Tissue destruction: Chronic activation of TLRs and the resulting inflammation can lead to tissue destruction and bone loss, a hallmark of periodontal disease. The pro inflammatory cytokines produced by activated immune cells can stimulate the production of matrix metallo proteinases (MMPs), enzymes that degrade extracellular matrix proteins, leading to the breakdown of periodontal tissues.
4. Inhibition of immune response: In some cases, bacterial components can inhibit the immune response by interfering with TLR signaling. For example, Porphyromonas gingivalis, a bacterium associated with periodontitis, produces an enzyme that cleaves TLR2 and TLR4, inhibiting the immune response and promoting bacterial survival. Overall, the activation of TLRs in response to bacteria is a critical step in the development of periodontal disease, and targeting TLRs may be a potential therapeutic approach for treating the disease.[8]

### *1.4. Strategies for down regulation of toll like receptor*

There are several strategies for down-regulating Toll-like receptors (TLRs) to potentially alleviate the chronic inflammation associated with TLR activation, including:

### *1.5. Small-molecule inhibitors*

Small-molecule inhibitors can block the activation of TLRs and downstream signaling pathways. For example, the TLR4 inhibitor eritoran has been tested in clinical trials for the treatment of sepsis and has shown promise in reducing inflammation.[9]

General mechanism for downregulating TLRs using small-molecule inhibitors:

Identification of Target: The first step in developing small-molecule inhibitors for TLRs is to identify the specific TLR or component of the TLR signaling pathway that needs to be targeted. Different TLRs recognize different PAMPs, so the choice of target depends on the disease or condition being treated.[10]

High-throughput Screening: Once the target is identified, researchers use high-throughput screening techniques to test thousands of small-molecule compounds for their ability to inhibit the target. This screening process helps identify potential lead compounds that show promising inhibitory activity.[11]

Hit Validation and Optimization: The lead compounds from the high-throughput screening are further validated to ensure their specificity and efficacy. Medicinal chemistry and structural biology techniques are employed to optimize the lead compounds for increased potency, selectivity, and bioavailability.

Mechanism of Action: Understanding the precise mechanism of action of the small-molecule inhibitor is crucial. It might involve direct binding to the TLR or its downstream signaling components, interfering with protein-protein interactions, or blocking enzymatic activity necessary for TLR signaling.[12]

Cellular and Animal Studies: The selected small-molecule inhibitors are then tested in cellular and animal models to determine their effectiveness in downregulating TLR signaling in a living system. These studies help establish the inhibitors' safety, efficacy, and potential side effects. If the small-molecule inhibitors show promising results in preclinical studies, they can progress to clinical trials involving human participants. These trials are designed to evaluate the compound's safety, dosage, and efficacy in treating specific diseases or conditions associated with TLR dysregulation.[13]

FDA Approval and Clinical Use: If the clinical trials demonstrate that the small-molecule inhibitor is safe and effective, it may receive approval from regulatory agencies such as the U.S. Food and Drug Administration (FDA) for clinical use. Once approved, the small-molecule inhibitor can be prescribed by healthcare providers to patients with relevant medical conditions.

It's important to note that the development of small-molecule inhibitors for TLRs is a complex and challenging process. Many factors, including specificity, bioavailability, and potential off-target effects, need to be carefully considered during the development process to ensure safe and effective therapeutic agents.[14]

## 2. Antibodies

Antibodies that specifically target TLRs can block their activation and downstream signaling pathways. For example, an anti-TLR2 antibody has been shown to reduce inflammation and bone loss in a mouse model of periodontitis.[15]

Here's a general mechanism of how these antibodies work:

Antibody Binding: TLR-specific antibodies are engineered to have high affinity and specificity for the target TLR. When introduced into the body, these antibodies circulate in the bloodstream and eventually encounter the TLRs present on the surface of immune cells, such as dendritic cells, macrophages, and B cells.[16]

Epitope Recognition: The antibodies bind to specific epitopes on the extracellular domain of TLRs. The epitope is a unique molecular structure or sequence that the antibody recognizes like a lock-and-key interaction. By binding to this specific epitope, the antibody prevents the TLR from interacting with its usual ligands, which are often pathogen-associated molecular patterns (PAMPs).[17]

Ligand Blockade: TLRs normally detect PAMPs from invading pathogens, such as bacteria, viruses, or fungi. When the antibodies bind to the TLRs, they physically block the binding site for PAMPs, preventing the TLRs from detecting these foreign molecules. As a result, the TLRs remain inactive and unable to initiate downstream signaling.[18]

Downstream Signaling Inhibition: TLR activation triggers a signaling cascade, leading to the activation of various transcription factors and the production of pro-inflammatory cytokines and other immune mediators. By blocking TLR activation, the antibodies also prevent the initiation of these downstream signaling pathways. This, in turn, helps to dampen the overall immune response and reduce inflammation.[19]

Immune Modulation: By inhibiting TLR activation and downstream signaling, the antibodies can help modulate the immune response. This modulation is beneficial in conditions where TLR-mediated inflammation contributes to autoimmune diseases, chronic inflammatory disorders, or excessive immune reactions.[20]

Clinical Applications: TLR-specific antibodies have shown promise as potential therapeutics for various autoimmune diseases, such as rheumatoid arthritis and

systemic lupus erythematosus, as well as inflammatory conditions like sepsis. Additionally, they can be used to study TLR functions and signaling pathways in both basic research and clinical settings. It's important to note that the development and use of TLR-specific antibodies require rigorous preclinical and clinical testing to ensure their safety, efficacy, and specificity. Moreover, the design of such antibodies demands a thorough understanding of TLR biology and the immune response to create effective therapeutic agents.[21]

## 3. Natural products

Some natural products have been shown to down-regulate TLRs and reduce inflammation. For example, curcumin, a compound found in turmeric, has been shown to inhibit TLR4 signaling and reduce inflammation in various animal models.

## 4. MicroRNA

MicroRNA (miRNA) are small non-coding RNA molecules that can regulate gene expression. Several miRNAs have been identified that target TLRs and down-regulate their expression. For example, miR-146a has been shown to down-regulate TLR4 and reduce inflammation in a mouse model of periodontitis.[22]

## 5. Nutritional Interventions

Some nutritional interventions have been shown to down-regulate TLRs and reduce inflammation. The activation of Toll-like receptors (TLRs) plays a significant role in the initiation and progression of inflammation in periodontitis. Nutritional interventions can help down-regulate TLRs and reduce inflammation in this condition. Here are some dietary strategies that may be beneficial:

Omega-3 Fatty Acids: Omega-3 fatty acids, found in fatty fish (such as salmon, mackerel, and sardines), flaxseed, chia seeds, and walnuts, have anti-inflammatory properties. They can help reduce the expression and activation of TLRs, leading to decreased inflammation in periodontitis. Antioxidant-Rich Foods: Foods high in antioxidants, such as fruits (berries, citrus fruits, and kiwi), vegetables (leafy greens, tomatoes, and bell peppers), and nuts (almonds and hazelnuts), can help combat oxidative stress and inflammation. Antioxidants can down-regulate TLRs and mitigate the immune response in periodontitis.[23] Probiotics: Probiotics, often found in yogurt and fermented foods, can positively influence the gut microbiota and, in turn, affect systemic inflammation. A healthy gut microbiota can help down-regulate TLR activation and reduce the inflammatory response in periodontitis. Vitamin D: Vitamin D is known to have immunomodulatory effects and can help regulate TLR expression. Adequate levels of vitamin D, obtained from sunlight exposure or dietary sources like fatty fish, egg yolks, and fortified foods, may help reduce inflammation in periodontitis.[24] Green Tea: Green tea contains catechins, which have anti-inflammatory properties. Drinking green tea regularly can help down-regulate TLRs and decrease inflammation in periodontitis. Curcumin: Curcumin, a compound found in turmeric, has potent anti-inflammatory effects.[25] It can inhibit TLR activation and reduce the production of pro-inflammatory cytokines, potentially alleviating inflammation in periodontitis.

Low Glycemic Index Diet: Consuming foods with a low glycemic index, such as whole grains, legumes, and non-starchy vegetables, can help regulate blood sugar levels and reduce the production of pro-inflammatory molecules associated with TLR activation.[26]

Avoiding Pro-Inflammatory Foods: Limiting the intake of processed foods, refined sugars, and unhealthy fats can help reduce overall inflammation in the body, including in the context of periodontitis. It's important to note that while nutritional interventions can support overall health and may help in reducing inflammation, they should not replace professional dental care for periodontitis management.[27] A holistic approach that combines proper nutrition, oral hygiene practices, and regular dental visits is essential for managing and preventing periodontal disease effectively. If you are considering dietary changes, it's a good idea to consult with a healthcare provider or a registered dietitian to tailor a plan that suits your individual needs and health conditions.[28–30]Overall, down-regulating TLRs is a promising therapeutic approach for reducing chronic inflammation associated with TLR activation. However, more research is needed to develop safe and effective strategies for down-regulating TLRs in humans.

## 6. Conclusion

Periodontal disease is a common inflammatory condition affecting the supporting structures of the teeth, including the gingiva, periodontal ligament, and alveolar bone. Toll-like receptors (TLRs) play a crucial role in the recognition of pathogen-associated molecular patterns (PAMPs) from bacteria that cause periodontal disease. The activation of TLRs triggers an inflammatory response intended to eliminate the bacteria and repair the damaged tissue. However, if the inflammation becomes chronic, it can lead to further tissue destruction and bone loss. In conclusion, TLRs play a critical role in the development of periodontal disease, and targeting these receptors may be a potential therapeutic approach for reducing chronic inflammation associated with the disease. Further studies are needed to fully elucidate the role of TLRs in periodontal disease and to develop effective therapeutic interventions.

## 7. Source of Funding

None.

## 8. Conflict of Interest

None.

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