SCIENTIFIC Publishing Limited

Trends in Immunotherapy
https://ojs.ukscip.com/index.php/ti

Review

Toll-like Receptors and Periodontitis: Current Insights into Immune Dynamics and Translational Therapeutics

Fong Fong Liew [1,*], Soon Hao Tan [2], Pallav Sengupta [3] and Sulagna Dutta [4,*]

[1] Department of Preclinical Sciences, Faculty of Dentistry, MAHSA University, Bandar Saujana Putra, 42610 Jenjarom, Selangor, Malaysia

[2] Department of Biomedical Science, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia

[3] Department of Biomedical Sciences, College of Medicine, Gulf Medical University, 4184 Ajman, United Arab Emirates

[4] Basic Medical Sciences Department, College of Medicine, Ajman University, 4184 Ajman, United Arab Emirates

[*] Correspondence: ffliew@mahsa.edu.my (Fong Fong Liew); sulagna_dutta11@yahoo.com (Sulagna Dutta)

Received: 22 July 2025; **Revised:** 31 July 2025; **Accepted:** 14 August 2025; **Published:** 7 January 2026

Abstract: Periodontitis is a common and persistent inflammatory disease resulting from a sophisticated relationship between oral bacteria and the body's immune system. Toll-like receptors (TLRs) act as crucial sensors within the immune response, playing a fundamental role in the disease's initiation and progression. This review examines periodontitis, highlighting the limited understanding of TLR activation mechanisms and the therapeutic potential of TLR inhibitors. The discussion begins with a definition of TLRs, outlining their characteristics, types, distribution, and activation mechanisms. It then details the manifestation of TLRs in periodontitis, including alterations during inflammation and their correlation with disease severity. TLR activity is influenced not only by microbial stimuli but also by epigenetic factors and miRNAs, which mediate gene expression changes linked to inflammation. Various miRNAs have been shown to regulate TLR signaling pathways, thereby modulating the inflammatory response in periodontal tissues. Additionally, epigenetic modifications further complicate the landscape of immune regulation in periodontitis, affecting TLR expression and function. This interplay between TLRs, miRNAs, and epigenetic changes underscores the systemic implications of periodontal disease, contributing to broader health issues. Consequently, the review explores innovative strategies to modulate TLR signaling and discusses future challenges in TLR research in relation to periodontitis treatment. In summary, a more profound understanding of TLR-driven immune responses, along with the regulatory roles of miRNAs and epigenetic factors, is essential for developing targeted therapies and advancing treatment options for periodontitis.

Keywords: Inflammation; Pathogen-Associated Molecular Patterns; Periodontitis; Toll-like Receptors; TLR2; TLR4

1. Introduction

Periodontitis (PD) is a common and long-standing inflammatory condition that gradually breaks down the tissues supporting the teeth, specifically the gums, periodontal ligament, and alveolar bone [1]. It affects a large portion of the population, with over half of adults over 30 and nearly 70% of seniors over 65 showing signs of the disease [2,3].

The disease often begins as gingivitis, an early inflammatory reaction to the accumulation of bacterial plaque. When this early stage is not resolved, it can escalate into chronic inflammation and irreversible tissue destruction [4,5]. What makes PD particularly challenging is its persistence, which is largely due to the body's inability to

turn off inflammation once it starts [6–8]. A major driver of this process is the entry of harmful bacteria into the gum tissues, which sets off a chain reaction of immune responses. This includes the recruitment of immune cells like neutrophils, macrophages, dendritic cells, and natural killer cells to the site of infection [9–12].

TLRs are essential elements of the innate immune system, functioning as pattern recognition receptors (PRRs) that have a critical role in identifying different microbial components referred to as pathogen-associated molecular patterns (PAMPs) [13]. The effectiveness of the immune system is dependent on the proper functioning of PRRs. The PRRs include TLRs, RIG-I-like receptors, Nod-like receptors (NLRs), AIM2-like receptors, C-type lectin receptors, and intracellular DNA and RNA sensors [14–16]. Once activated by microbial signals, TLRs trigger pathways such as nuclear factor kappa B (NF-κB) and type I interferon (IFN) that drive inflammation and help initiate adaptive immunity [15,17–19].

In the oral environment, where the immune system is constantly exposed to bacteria, TLRs are vital for maintaining balance. They help distinguish between harmless microbes and harmful pathogens and coordinate appropriate responses [20]. However, when this delicate balance is disrupted, especially by bacteria such as *Porphyromonas gingivalis*, known to promote microbial imbalance (dysbiosis), it will lead to chronic disease [21].

The resulting inflammation damages both soft and hard tissues, fueled by a complex mix of signaling molecules and immune cells [4,22–26]. Neutrophils, in particular, are highly active in PD and can be stimulated by both TLRs and complement pathways, such as complement component 5a [27]. In addition to innate immunological sensing through TLRs, neutrophil activation can also take place through other mechanisms. Due to a lack of neutrophil recruitment [28] and dysregulated Th17 immunity, individuals who have leukocyte adhesion disease type 1 are more likely to develop periodontal disease and have severe symptoms of the illness. This is because of the increased oral bone loss that occurs as a result of bacterial infection [29].

While TLRs offer promising potential as therapeutic targets, their essential role in defending the host complicates the development of treatments. Broadly blocking TLR function could leave the body more vulnerable to infection. However, selectively modulating specific TLRs may provide a safer, more effective way to manage periodontal inflammation [30,31].

Despite growing interest in the role of TLRs in periodontitis, the molecular mechanisms underlying their activation and regulation remain poorly defined. The complicated relationship between microbial dysbiosis, immune cell dysfunction, and TLR signaling represents a significant yet underexplored area in periodontal research. While several previous reviews have addressed aspects of TLR function, most have focused broadly on innate immunity or predate recent advances in TLR-targeted therapies.

This review addresses critical gaps in the TLR-associated research. It integrates the latest insights into the signaling within the specific context of dysbiotic microbial communities and immune dysregulation in PD, emphasizing the dual role of TLRs in both preserving oral immune homeostasis and driving chronic inflammation—a perspective often underrepresented in earlier work. Additionally, this review explores the translational relevance of selectively modulating TLR activity, highlighting emerging therapeutic strategies and identifying key directions for future research. By bridging fundamental immunological mechanisms with clinical application, this work provides an updated and clinically meaningful perspective on TLRs in PD, with implications for both local disease control and broader systemic health.

2. Distribution and Expression of Toll-like Receptors in Immune Cells

TLRs are a critical subset of PRRs that initiate innate immune responses. These transmembrane proteins are characterized by extracellular leucine-rich repeat (LRR) domains responsible for pathogen recognition, and intracellular Toll/interleukin-1 receptor (TIR) domains essential for downstream signaling. Upon ligand recognition, TLRs initiate pro-inflammatory cytokine and IFN production through adaptor proteins, forming a primary defense mechanism. This signaling is tightly regulated by feedback mechanisms to prevent excessive inflammation and maintain immune homeostasis. Dysregulated TLR signaling is implicated in chronic inflammatory and autoimmune diseases, which highlights the therapeutic promise of TLR modulation [19,20,32–36].

TLRs are unevenly distributed inside a cell and classified based on their specific position within the cell. TLRs are synthesized in the endoplasmic reticulum, processed through the Golgi apparatus, and transported to either the plasma membrane (TLR1, 2, 4, 5, 6, 10) or endosomal compartments (TLR3, 7, 8, 9) [37–39]. Human TLR genes are mapped to specific chromosomal locations: TLR1 and TLR6 reside proximal to 4p14, TLR2 is situated at 4q32,

TLR3 occupies 4q35, TLR4 is located at 9q32-33, TLR5 is found at 1q33.3, and TLR7 and TLR8 are co-located at Xp22. TLR9 claims its position at 3p21.3 [19,40,41]. In contrast, mice possess TLR1–TLR13, with TLR10 being non-functional [40,41]. The TLR family in humans consists of 10 distinct members (TLR1-TLR10), each possessing remarkable capabilities to recognize unique PAMPs associated with various pathogens [19]. Mammals contain a total of 13 TLRs, specifically TLR1-13. However, humans only have 10 of these receptors (TLR1-10), whereas mice have all 13, but TLR10 is not functional [39,42].

TLRs are differentially expressed across immune and non-immune cells, contributing to host defense. Monocytes and macrophages express most TLRs except TLR3. Myeloid dendritic cells (MDCs) express TLR1, 2, 4, 5, and 8, enabling detection of diverse pathogens. Plasmacytoid dendritic cells (PDCs), which make up a small fraction of blood mononuclear cells, express only TLR7 and TLR9, allowing them to detect viral nucleic acids and trigger antiviral responses via myeloid differentiation primary response 88 (MyD88), TRAF6, IRF-7, and IRAK4 signaling pathways [43–45]. TLR4 signaling in MDCs involves MAP3K apoptosis signal-regulating kinase 1 for cytokine secretion. Restoring dendritic cells (DCs) function using factors like Fms-related tyrosine kinase 3 ligand enhances immune responses and survival in septic models. TLR agonists also show promise in reversing immunosuppression and preventing secondary infections [46,47].

Dendritic cells (DCs), renowned for their role in antigen presentation, contribute significantly to the landscape. MDCs express a spectrum of TLRs, including TLR1, TLR2, TLR4, TLR5, and TLR8. This array equips MDCs to detect a wide range of pathogenic signatures, initiating immune responses. In contrast, PDCs express exclusively TLR7 and TLR9, suggesting a dedicated role in detecting viral nucleic acids and modulating antiviral defenses [45]. PDCs, comprising a small percentage of blood mononuclear cells, release various cytokines upon pathogen exposure through TLR7 and TLR9 activation, mediated by MyD88, TRAF6, IRF-7, and IRAK4 [43,44]. Different subtypes of MDCs express various TLRs, except TLR9 [46,48].

Gamma delta (γδT) cells, key players in the innate immune system, contribute to pathogen defense, immune regulation, and tissue homeostasis. In humans, they are classified into Vδ1 and Vδ2 subsets; Vδ1 cells reside mainly in mucosal tissues, while Vδ2 cells circulate in peripheral blood [49]. Sepsis leads to a decline in Vδ2 γδT cells, especially $CD3^+CD56^+$ subsets, correlating with disease progression and organ injury in animal models [50]. γδT cell activation is partly mediated by TLRs, with TLR1, TLR2, TLR4, TLR5, and TLR6 variably expressed on peripheral γδT cells [50–55]. TLR3 expression is induced by TCR stimulation, not by TLR3 ligands, while TLR7 and TLR8 are intracellular; TLR9 remains undetectable. These findings highlight the role of γδT cells in TLR-driven innate immune responses.

T cells, central to adaptive immunity, play diverse roles in inflammation. In sepsis, rapid apoptosis of $CD4^+$ and $CD8^+$ T cells occurs within 24 hours, and blocking this apoptosis may restore protective immunity [56,57]. Regulatory T cells (Tregs) increase during sepsis, potentially impairing tissue protection. While adoptive Treg transfer enhances TNF-α release and survival, Treg depletion after three days improves outcomes. TLR2, TLR3, TLR4, TLR5, and TLR9 show differential expression across $CD4^+$ and $CD8^+$ T cells, modulated by TCR signaling and mouse strain [57–60].

B cells contribute to early innate responses in bacterial sepsis beyond antibody production. B–cell–deficient mice exhibit impaired cytokine responses and higher mortality [60]. Human and murine B cells show distinct TLR2 and TLR4 responses [60–62]. TLR9 activation influences vaccine-related antibody responses, and TRAF5 regulates B cell TLR signaling. TRAF5 deficiency enhances mitogen-activated protein kinases (MAPK) activation and increases IL-6, IL-12p40, IL-10, TNF-α, and IgM production [63]. IL-10–producing regulatory B cells are reduced in autoimmune diseases such as rheumatoid arthritis (RA), pemphigus vulgaris, multiple sclerosis (MS), inflammatory bowel disease (IBD), type 1 diabetes mellitus (T1DM), and systemic lupus erythematosus (SLE) [63,64]. Elucidating TLR signaling in B cells offers potential for novel therapies in inflammatory disorders.

Mast cells, key players in immune and allergic responses, express TLR2, TLR4, TLR6, and TLR8, but lack TLR5, suggesting unique regulatory mechanisms [65,66]. Ligands such as lipopolysaccharide (LPS), lipoteichoic acid (LTA), and peptidoglycan (PGN) trigger mast cell secretion of TNF-α, IL-5, IL-10, and IL-13 [67]. In murine mast cells, TLR4 signaling occurs via the MyD88 pathway, while TIR domain-containing adaptor inducing interferon-β (TRIF) is inactive. Human mast cells also express TLR1, TLR3, TLR5, and TLR6–10 at the mRNA level. TLR3 stimulation by poly I:C induces IFN-α/β release, though mouse mast cell responses to TLR3, TLR7, and TLR9 vary significantly [68–71]. TLR4 recognizes LPS in conjunction with co-receptors such as CD14 and MD-2, whereas RP105

modulates TLR4-mediated LPS responses [32,33].

Epithelial cells, critical at barrier sites, exhibit tissue-specific TLR expression. Intestinal epithelial cells express TLR5 on the basolateral surface, aiding in pathogen detection beyond the barrier, while TLR4 is upregulated in inflammatory bowel disease. Renal epithelial cells express TLR2 and TLR4, contributing to bacterial defense and inflammation [20,72].

Beyond immune cells, corneal epithelial cells express TLR4, aiding defense against parasitic infections, and endothelial cells (ECs) express TLR4, detecting pathogens and triggering immune responses [20,73]. While monocytes/macrophages respond to LPS or Pam3Cys by releasing TNF-α and IL-1β, ECs induce IL-6, IL-8, CSF2/3, ICAM-1, and SELE via ERK1/2 and ERK5 pathways. MEK1 inhibits TLR2 signaling in ECs but promotes it in monocytes. ECs also express TLR2 and TLR4 intracellularly and release distinct cytokines, influencing diseases such as sepsis-induced vascular leakage and chronic inflammation [74,75].

Microglia and astrocytes, key immune cells in the brain, express TLRs that mediate pathogen recognition and drive neuroinflammation in neurodegenerative diseases and stroke [76]. Microglia upregulate TLR1–9 and CD14 in response to infection. Astrocytes express TLR1, TLR2, TLR3, TLR5, TLR7, TLR8, and TLR9, though TLR4 expression remains debated. They also contain TLR signaling adaptors such as MyD88, TIRAP, and TRIF, enabling them to complement microglial responses in CNS inflammation, including sepsis [77–80].

Platelets, beyond hemostasis, participate in angiogenesis, antimicrobial defense, and neurodegeneration [81,82]. Platelet-expressed TLR1, TLR2, TLR4, TLR6, and TLR9 mediate responses in sepsis, influenza, transfusion injury, and cardiovascular disease [83]. TLR activation promotes platelet inflammation and thrombin generation, with TLR2 implicated in histone-induced coagulation and TLR4 polymorphisms linked to reduced cardiovascular risk [84]. This diversity in TLR expression across cell types reflects the immune system's complex and adaptable defense strategies.

3. TLR Expression in Periodontal Tissues

TLRs are differentially expressed across immune and non-immune cells and play essential roles in maintaining immune balance. Dysregulated TLR signaling is linked to chronic inflammation and autoimmune diseases. Investigating TLR expression in periodontal tissues is important, as their activation by oral pathogens contributes to the inflammation and tissue damage seen in periodontitis. Understanding their local expression and function could guide targeted therapies to modulate immune responses and control disease progression. **Table 1** provides a comprehensive overview of TLR isoforms, detailing their active forms, cellular localization, expression patterns in periodontitis, associated cell types, and immunological functions. It highlights the diverse roles of individual TLRs in recognizing microbial components and orchestrating host immune responses within periodontal tissues. **Table 2** provides further information on the strengths, limitations, and potential of each TLR dimer.

Focusing on TLR expression in periodontal tissues is essential for understanding the early pathogenesis of periodontitis. Gingival epithelial cells and fibroblasts, as key resident cells, form the first line of defense by recognizing microbial patterns through TLRs and initiating local inflammatory responses. Upon activation, these TLRs trigger signaling pathways that lead to the release of pro-inflammatory cytokines, antimicrobial peptides, and matrix metalloproteinases, contributing to epithelial barrier disruption, connective tissue breakdown, and altered bone remodeling via the RANKL/OPG axis—mechanisms critical in the early and progressive stages of disease [85,86]. Unlike studies centered on immune cells such as macrophages and neutrophils, which are recruited later, tissue-level analysis captures the early molecular events that shape the local disease environment. Moreover, evidence from longitudinal studies in nonhuman primates shows that TLR expression in gingival tissues fluctuates dynamically during disease initiation and resolution, often independently of immune cell infiltration [30,85]. Therefore, examining TLR activity in epithelial and fibroblast populations offers deeper insight into the mechanisms of disease onset and progression and may uncover novel therapeutic targets [87–89].

Beyond epithelial and immune cells, TLR expression has been identified in various oral-derived mesenchymal stromal cells, including human periodontal ligament stem cells (hPDLSCs) [90], dental pulp stem cells (DPSCs) [90], human gingival mesenchymal stem cells (hGMSCs) [91], bone marrow mesenchymal stem cells (BM-MSCs) [92], and stem cells of the apical papilla [93]. While immune cells play a key role in pathogen recognition and clearance through TLR-mediated cytokine production and phagocytosis, resident stromal and epithelial cells are central to initiating localized immune responses.

In periodontal diseases such as gingivitis and periodontitis, microbial pathogens trigger increased TLR expression across multiple cell types, contributing to the inflammatory cascade. TLR2 and TLR4 are particularly important in recognizing bacterial components like LPS and LTA in periodontal biofilms [94,95].

This activation initiates intracellular signaling cascades, including NF-κB and interferon regulatory factors (IRF) pathways, resulting in the production of pro-inflammatory mediators, recruitment of neutrophils, and tissue destruction. Elevated TLR2 and TLR4 mRNA levels have been observed in patients with chronic periodontitis [96], with *P. gingivalis* shown to activate these pathways and enhance monocyte-derived chemokine production [97,98].

TLR9, a DNA-sensing receptor, also plays a role in periodontal inflammation by detecting unmethylated CpG motifs in bacterial DNA. Its activation promotes osteoclastogenesis and bone resorption, key features of advanced periodontitis [99, 100]. Increased TLR9 expression in inflamed gingival tissues has been linked to age-related inflammatory conditions, including cerebral amyloid deposition and skeletal muscle fibrosis [101–103]. Despite these associations, the exact mechanisms by which TLR9 interacts with microbial or damage-associated signals in aging oral tissues remain unclear.

Additionally, some pathogens can subvert TLR signaling to evade immune detection, while host factors such as genetic background and systemic health influence TLR function. Dysregulation of TLR pathways may create a vicious cycle of unresolved inflammation, excessive tissue destruction, and progressive alveolar bone loss, underscoring the importance of balanced TLR signaling in maintaining periodontal health. These findings open exciting possibilities for new therapeutic approaches in managing periodontitis, particularly by targeting specific TLR2, TLR4, and TLR9. By understanding how these receptors drive inflammation and tissue breakdown, researchers can begin to design treatments that not only stop disease progression but also promote healing.

Table 1. TLR characteristics and immunological functions in periodontal inflammation.

No	TLR	TLR Active Form	Location	Location of Expression in Periodontitis	Cell Types	Function	Refs
1	TLR1 (CD281)	TLR1-TLR2	Type 1 transmembrane receptor	Epithelial cells Gingival fibroblasts	These include white blood cells, natural killer cells, resting B cells, γδT cells in the peripheral blood of humans, platelets, CD4+ T cells, microglia, astrocytes, and immature dendritic cells.	Recognizes and contributes to Gram-positive bacterial lipoproteins. TLR1 triggers intracellular signaling cascades, resulting in an inflammatory response and the activation of immunological responses.	El-Zayat et al. [33], Beklen et al, [104], Janssens & Beyaert [105], Han et al. [106], Vijay [107]
2	TLR2 (CD282)	TLR1-TLR2 TLR2-TLR2 TLR2-TLR6 TLR2-TLR10	Type 1 transmembrane receptor	Monocytes, Macrophages	Airway epithelium, lung alveoli, renal tubules, and the Bowman's capsules inside renal corpuscles. Peripheral blood leukocytes, microglia, Schwann cells, monocytes, macrophages, dendritic cells, B cells, and T cells. Mononuclear cells, keratinocytes, sebaceous glands, and intestinal epithelial cells.	Detects Gram-positive and Gram-negative bacteria, fungi, viruses, and certain endogenous chemicals. Typically, this leads to the absorption of attached molecules by endosomes/phagosomes and the activation of cells.	Beklen et al. [104], Janssens & Beyaert [105], Vijay [107], Cario [108], Sepehri [109]
3	TLR3 (CD283)	TLR3-TLR3	Endoplasmic reticulum, lysosomal membrane	Epithelial cells Dendritic cells	Macrophages, placenta, pancreas, and iDC (CD11c+iDC).	Recognizes double-stranded RNA, which is commonly generated during viral infections, and initiates an immune response to combat the virus. TLR3 triggers the activation of IRF3, leading to an increase in the production of type I interferons. These interferons then communicate with other cells, prompting them to enhance their antiviral defenses.	Beklen et al. [104], Vijay [107], Han et al. [110], Alexopoulou et al. [111]
4	TLR4 (CD284)	TLR4/MD2–TLR4/MD2 TLR4-TLR6	Cell membrane, endoplasmic reticulum, lysosomal membrane	Monocytes, Macrophages, Dendritic cells	Myeloid-derived immune cells, such as monocytes, macrophages, and dendritic cells. Epithelium, endothelium, placental cells, and beta cells in Langerhans islets.	The immune system launches an attack against Gram-negative bacteria when it detects LPS on their cell walls. In order to help eliminate the invading bacteria, TLR4 reacts to LPS in tissues and the circulation during infection, setting off pro-inflammatory responses.	Beklen et al. [104], Vijay [107], Vaure et al. [112]
5	TLR5 (CD285)	TLR5-TLR5	Cell membrane	Epithelial cells, Gingival fibroblasts	Monocytes, PreDC, and iDC (CD11c+iDC), gingival epithelial cells.	Through direct interaction, Caveolin-1 has the ability to stabilize TLR5, increasing the level of TLR5. Detects bacterial flagellin, a protein present in bacterial flagella, and aids in the immune response against moving germs.	Beklen et al. [104], Miao et al. [113], Lim et al. [114]
6	TLR6 (CD286)	TLR2-TLR6 TLR4-TLR6	Cell membrane	Epithelial cells, Gingival fibroblasts	B lymphocytes, dendritic cells, microglia, macrophages, neutrophils, NK cells, and monocytes. Appendix, spleen, and lymph node.	TLR2 forms heterodimers with it and detects diacylated lipopeptides from Gram-positive bacteria.	Beklen et al. [104], Noreen & Arshad [115], Yeh et al. [116], Kang et al. [117]
7	TLR7 (CD287)	TLR7-TLR7	Cell membrane, endoplasmic reticulum, lysosomal membrane	Epithelial cells, Plasmacytoid. dendritic cells	Macrophages, NK cells, resting B cells, germinal center B cells, and plasmacytoid DC. In lung, placenta, and spleen.	Detect single-stranded RNA, often from viruses.	Beklen et al. [104], Janssens & Beyaert [105], Jackson & Rovin [118], Brown et al. [119]
8	TLR8 (CD288)	TLR8-TLR8	Endoplasmic reticulum, lysosomal membrane	Monocytes, Macrophages, Dendritic cells	Lung and peripheral blood leukocytes, neutrophils, Monocytes, resting B cells, germinal center B cells, preDC (Monocytes), iDC (CD11c+iDC).	In mice, it is not functioning. Identify single-stranded RNA, which is often produced by viruses.	Beklen et al. [104], Janssens & Beyaert [105], Heil et al. [120], Huang et al. [121]

Table 1. *Cont.*

No	TLR	TLR Active Form	Location	Location of Expression in Periodontitis	Cell Types	Function	Refs
9	TLR9 (CD289)	TLR9-TLR9	Endoplasmic reticulum, lysosomal membrane	Plasmacytoid, dendritic cells	Dendritic cells, macrophages, natural killer cells and other antigen-presenting cells.	The immunological response is triggered by unmethylated CpG DNA patterns that are present in bacterial and viral DNA.	Beklen et al. [104], Janssens & Beyaert [105], Leite et al. [122], Lund et al. [123]
10	TLR10 (CD290)	TLR1-TLR10 TLR2-TLR10 TLR10-TLR10	Cell membrane, endoplasmic reticulum, lysosomal membrane	Monocytes, Macrophages, Dendritic cells	Resting B cells, Germinal c B cells, iDC (CD11c+iDC), spleen, lymph nodes and tonsils.	Exhibiting an anti-inflammatory role as opposed to a pro-inflammatory one.	Beklen et al. [104], Janssens & Beyaert [105], Leite et al. [122], Hess et al. [124]

Table 2. Preclinical and clinical studies for TLR dimers.

TLR	TLR Active Form	Preclinical Evidence	Clinical Evidence	Strengths	Limitations	Translational Potential	Refs
TLR1	TLR1-TLR2	Recognizes triacylated lipopeptides, activating MyD88–NF-κB/MAPK pathways in macrophages, dendritic cells, and epithelium. Mouse models show roles in bacterial clearance and inflammation; blockade reduces inflammatory damage in some infections and periodontitis models.	Elevated expression in inflamed tissues and blood leukocytes. SNPs linked to infection risk and cytokine response variability, including in periodontitis. No large-scale trials directly targeting TLR1/2; most translation via TLR2-focused adjuvants or antagonists.	Clear ligand specificity, well-mapped signaling, and structural data support drug design, relevant at multiple mucosal sites.	Functional overlap with TLR2/TLR6, species differences in responses	Biomarker for inflammatory status; agonists for vaccines or antagonists for chronic inflammation; structural insights enable rational therapeutic design, but safety concerns remain.	Kang et al. [117], Shukla et al. [125], Sahasrabudhe et al. [126], Raieli et al. [127], Zhu et al. [128], Plantinga et al. [129], Monlish et al. [130], Su et al. [131], Takeuchi et al. [132]
TLR2	TLR2-TLR2	Homodimerization is reported *in vitro,* but functional signaling as a pure TLR2 homodimer is weak/controversial; most activity requires a TLR1/6 partner or co-receptor.	Sparse direct clinical evidence for TLR2 homodimer function; TLR2 expression is upregulated in many inflammatory conditions.	Studies collectively reveal TLR2's varied and significant roles in mediating immune responses across many diseases. These findings provide a strong foundation for understanding TLR2's functions in health and disease.	Many studies are limited by their focus on specific pathways, disease models, or populations. *In vivo* studies frequently employ animal models that might not fully represent human immunological responses or disease states.	It requires more mechanistic validation.	Yang et al. [133], Frank et al. [134], Weinkove et al. [135], Kwok et al. [136], Soberman et al. [137]
TLR3	TLR3-TLR3	Detects viral dsRNA and poly I:C via TRIF, inducing type I IFNs and cytokines. Knockouts show reduced antiviral defense. Poly I:C boosts NK and CD8+ T cells in cancer models but can worsen CNS inflammation.	Expressed in epithelial cells, DCs, fibroblasts, and neurons. Loss-of-function variants linked to herpes encephalitis and upregulated in viral infections, autoimmune diseases and cancers. Poly I:C trials show immune activation but also toxicity.	Diverse roles in antiviral defense, autoimmune regulation, and cancer immunity, with strong links to key signaling pathways for therapy development.	Most research uses pathogen-specific or preclinical models that may not reflect human disease, and TLR3 signaling remains complex and incompletely understood.	TLR3 shows promise for vaccines, infection control, and cancer therapy, but further research is needed.	Alexopoulou et al. [111], Tsai et al. [138], Lim et al. [139], Chen et al. [140]
TLR4	TLR4/MD2–TLR4/MD2	Recognizes LPS from Gram-negative bacteria via MD-2 and CD14, activating MyD88/TRIF pathways. Knockouts show resistance to LPS shock but higher infection susceptibility. Antagonists reduce inflammation in sepsis models.	Widely expressed on immune and endothelial cells. High levels in sepsis, atherosclerosis, periodontitis, and metabolic disease. Genetic variants linked to infection and CVD risk. Eritoran is safe in trials, but no mortality benefit in sepsis.	Well-characterized structure and ligand binding; strong *in vivo* proof; broad disease relevance, including infections, inflammation, neurocognitive disorders, and cardiovascular diseases.	Strong inflammatory potential; systemic antagonism may impair bacterial defense; many studies are limited by their focus on specific pathogens, conditions, or cell types.	Targeting the TLR4/MD2 complex holds strong potential for therapies in inflammation, cancer, and neuroprotection, but further research is needed to clarify mechanisms and expand clinical use.	Park & Lee [141], Opal et al. [142], den Dekker et al. [143], Oliveira et al. [144], O'Neil et al. [145], Xu et al. [146], Zuo et al. [147]
	TLR4-TLR6	Limited *in vitro* evidence suggests possible TLR4–TLR6 cooperation in recognizing atypical bacterial ligands; no robust animal model confirmation.	No direct human clinical studies; expression co-detection in some inflammatory tissues, but functional relevance unclear.	Potential to broaden TLR4 ligand recognition spectrum; theoretical synergy could enhance pathogen sensing and immune activation.	Unknown signaling dominance	Lack of functional confirmation.	Stewart et al. [148], Shmuel-Galia et al. [149]
TLR5	TLR5-TLR5	TLR5 homodimers specifically detect bacterial flagellin, leading to the activation of NF-κB and the subsequent production of pro-inflammatory cytokines. Studies have demonstrated their role in enhancing mucosal immunity in mouse models.	Elevated expression levels of TLR5 have been observed in conditions such as inflammatory bowel disease, chronic obstructive pulmonary disease, and certain cancers. Additionally, flagellin-based vaccines are being trialed for their potential in infection prevention.	TLR5 exhibits highly specific ligand recognition for flagellin, plays a significant role in mucosal immunity, and has promising applications as a vaccine adjuvant.	Overactivation of TLR5 has been associated with chronic inflammatory responses. Additionally, there is limited data on the long-term modulation of TLR5 activity in humans, and notable species differences exist in TLR5 responses.	TLR5 shows promising potential for use as a vaccine adjuvant and in enhancing mucosal immunity. It may also serve as a therapeutic target in the treatment of chronic infections and cancer immunotherapy.	Zhou et al. [150], Zhao et al. [151], Treanor et al. [152], Gewirtz et al. [153], Afzal et al. [154]
TLR6	TLR2-TLR6	Recognizes diacylated lipopeptides. Mouse and cell models show TLR2–TLR6 drives cytokine production and contributes to bacterial clearance and inflammatory pathology.	Elevated in inflamed tissues; some SNPs are linked to infection risk, but limited intervention data.	Distinct ligand specificity; clear MyD88 signaling pathway.	Functional overlap with other TLR2 heterodimers	Suitable for selective antagonists or modulators in diseases driven by diacyl lipopeptides, but requires careful patient stratification and human-centric validation.	Kang et al. [117], Takeuchi et al. [155], Love et al. [156]
TLR7	TLR7-TLR7 TLR7-TLR8	An intracellular protein that detects viral RNA and synthetic drugs, triggering a signaling pathway that produces type I interferons to fight viruses and enhance anti-cancer immunity.	Imiquimod approved for warts/BCC; TLR7/7–8 agonists in cancer trials show immune activation but dose-limiting toxicity.	Clear ligand biology and conserved signaling; proven ability to elicit strong type I IFN responses useful for antiviral and antitumor immunity; existing approved topical agent (imiquimod) demonstrates clinical feasibility.	Risk of inflammation; murine–human differences; possible off-target effects.	High for topical/local use and vaccine adjuvants; moderate for systemic use due to safety concerns.	Heil et al. [120], Diebold et al. [157], Adams et al. [158], Frega et al. [159]

Table 2. *Cont.*

TLR	TLR Active Form	Preclinical Evidence	Clinical Evidence	Strengths	Limitations	Translational Potential	Refs
TLR8	TLR8-TLR8 TLR7-TLR8	TLR8 recognizes ssRNA and various synthetic agonists, leading to the activation of the MyD88 pathway, which in turn activates NF-κB and IRF7. Murine models exhibit less active TLR8.	Clinical trials have investigated TLR8 agonists, such as motolimod, in the context of cancer and viral infections. While these trials demonstrated immune activation, the overall efficacy was limited, and some patients experienced systemic toxicity.	TLR8 serves as a potent inducer of Th1-type immune responses and exhibits synergistic effects when combined with other TLRs. This characteristic makes TLR8 a promising candidate for inclusion in vaccine formulations and cancer immunotherapy strategies.	The narrow therapeutic window for TLR8 activation poses a toxicity risk. Furthermore, significant species differences in TLR8 activity challenge the reliability of preclinical models, as systemic activation can lead to excessive inflammatory reactions.	High for vaccine adjuvants and targeted cancer immunotherapy; systemic applications constrained by safety profile.	Paul et al. [160], Bender et al. [161], Finberg et al. [162], Kawai & Akira [163], Wang et al. [164], Urban-Wojciuk et al. [165], McGowan et al. [166]
TLR9	TLR9-TLR9	Detects unmethylated CpG DNA, activating MyD88–NF-κB/IRF7 to induce IFN-α and cytokines, driving anti-pathogen, antitumor, and autoimmune responses.	CpG oligodeoxynucleotides evaluated as vaccine adjuvants, cancer immunotherapy agents, and antiviral treatments; effective immune activation in trials, but mixed efficacy and some adverse inflammatory reactions.	A promising target for therapeutic interventions in diverse fields, from oncology to infectious diseases.	Context-specific findings and reliance on animal models may limit human applicability.	Strong potential for vaccines, immunotherapies, and chronic inflammation treatments; broader clinical validation needed.	Jin et al. [167], Kumagai et al. [168], Babenko et al. [169], Jeon et al. [170], Wagner et al. [171]
TLR10	TLR1-TLR10	Very limited *in vitro* evidence; hypothesized to form non-canonical complexes that may modulate TLR1/2 signaling—no robust animal data due to TLR10 being nonfunctional in mice.	No direct clinical functional studies; some genetic association data hint at TLR10 loci affecting inflammatory disease risk.	It could fine-tune TLR1-driven responses; human-specific biology may reveal novel regulatory mechanisms.	Practically untested *in vivo*.	Requires human cell-based and *ex vivo* validation before therapeutic work.	Guan et al. [172], Su et al. [173]
	TLR2-TLR10	*In vitro* data show TLR10 can heterodimerize with TLR2 and suppress TLR2-driven cytokine responses; limited human primary-cell studies suggest inhibitory signaling. No reliable murine models.	TLR10 is expressed in B cells and pDCs; SNPs in the TLR10 locus are associated with an altered risk of Crohn's disease, RA, and other inflammatory conditions in some cohorts—no therapeutic trials.	It could be an endogenous brake on TLR2-mediated inflammation.	Mechanism incompletely defined.	Promising for human-targeted anti-inflammatory biologics if the mechanism and safety are confirmed in *ex vivo*/humanized models.	Oosting et al. [174], Hasan et al. [175], Fore et al. [176]
	TLR10-TLR10	*In vitro* antibody engagement or overexpression shows TLR10 homodimers suppress NF-κB/MAPK/Akt signaling in human monocytes, B cells, and pDCs; humanized mice confirm anti-inflammatory role.	Expression in human immune cells has been documented; associations of TLR10 variants with clinical phenotypes have been reported but are inconsistent.	Potent human-specific anti-inflammatory regulator; antibody targeting modulates key pathways while preserving antimicrobial function.	Lack of *in vivo* validation and limited reproducible functional assays.	Requires robust mechanistic and safety data from human-cell systems or humanized models before drug development.	Oosting et al. [174], Hess et al. [177], Deb et al. [178], Sindhu et al. [179]

4. TLR as Key Mediators of Local and Systemic Inflammation in Periodontitis

TLRs play a central role in the immune response to periodontitis, which is driven by microbial dysbiosis in the periodontal biofilm, which activates host cells and initiates inflammation that can lead to tissue destruction and tooth loss [30,180]. Upon activation, TLRs initiate intracellular signaling pathways—most notably NF-κB and MAPK—leading to the release of pro-inflammatory cytokines and chemokines [181]. While this response is critical for controlling infection, it can also contribute to tissue damage. Immune cells like neutrophils and macrophages release reactive oxygen species and proteolytic enzymes, which exacerbate connective tissue breakdown [4, 13]. Importantly, TLR-mediated inflammation is not limited to the oral cavity. Inflammatory mediators such as IL-6 and TNF-α can enter systemic circulation, contributing to chronic conditions including cardiovascular disease, diabetes, and adverse pregnancy outcomes [4,180,182,183]. This highlights the broader health implications of periodontitis and the role of TLRs in linking oral and systemic inflammation. Modulating their activity could provide novel approaches for both local disease management and reducing systemic inflammatory burden.

Two major pathways are activated: The MyD88-dependent and TRIF-dependent pathways. The MyD88-dependent pathway, triggered by TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10, will recruit adaptor proteins such as IRAK and TRAF6. This activation leads to the stimulation of key transcription factors, particularly NF-κB and MAPK, promoting the transcription of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α [20,184].

TLR engagement also promotes the generation of reactive oxygen species and nitric oxide, contributing to oxidative stress and subsequent tissue damage in the periodontium [20,185]. Beyond innate immunity, TLR signaling influences adaptive responses by enhancing antigen presentation and promoting T and B cell activation [186,187]. However, this response must be finely regulated. Host factors such as genetic polymorphisms, age, and systemic health can significantly alter TLR expression and responsiveness, predisposing individuals to exaggerated immune activation and chronic inflammation [188,189].

Importantly, TLRs function as immune sentinels but also exhibit a dual role in disease progression. Dysregulated or prolonged TLR signaling can perpetuate a vicious cycle of inflammation and tissue destruction, not only in periodontitis but across various autoimmune and chronic inflammatory diseases [190]. Understanding this duality

is crucial for developing precision therapies that modulate TLR signaling to restore immune homeostasis [191].

Upon ligand binding, TLRs activate transcription factors such as IRFs and NF-κB, which promote the production of immune effectors like type I interferons and pro-inflammatory cytokines [34,35]. These responses are coordinated through key adaptor proteins within the TLR signaling network, as depicted in **Figures 1** and **2**. The core components of this signaling network consist of adaptor molecules, including MyD88 and TRIF. MyD88 transduces signals from TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10, while TRIF coordinates signals from TLR3, TLR7, TLR8, and TLR9 [192,193]. Supplementary pathways such as MAPK and PI3K refine the signaling response, enabling fine-tuned control of chemokines, cytokines, and other immune effectors [194].

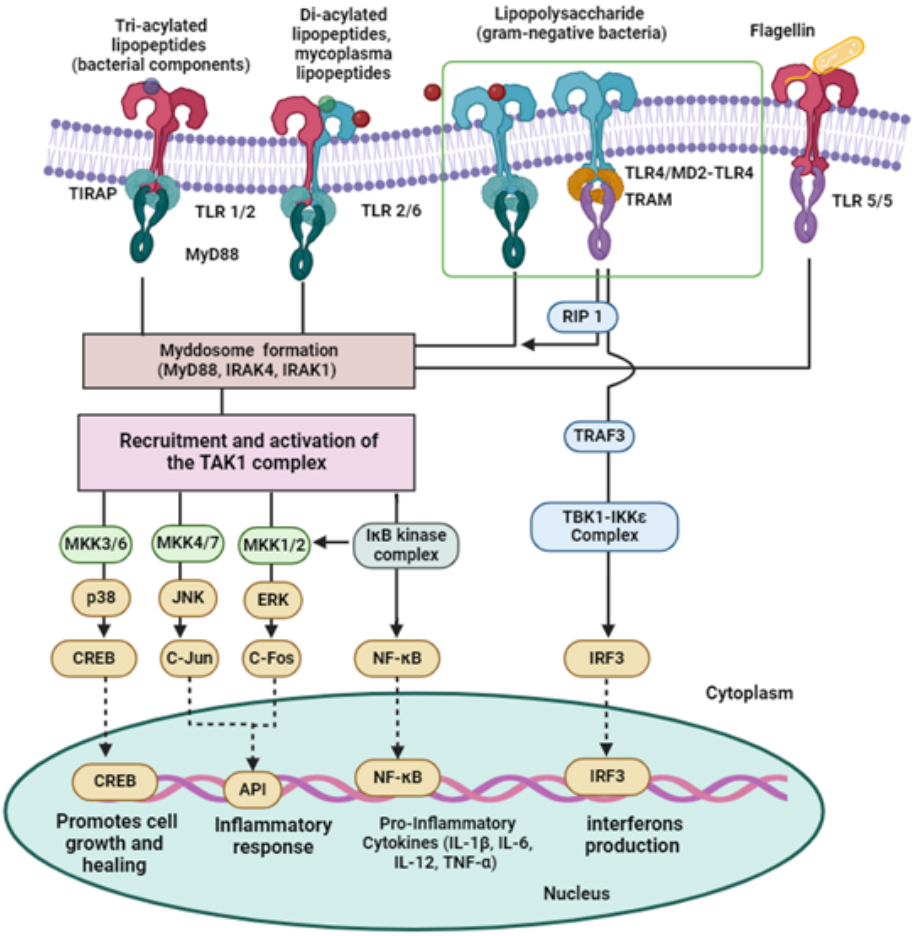

Figure 1. The Toll-like receptor (TLR) signaling pathway.

Notes: The Toll-like receptor (TLR) signaling pathway in innate immune cells involves receptors located at the cell surface or within endosomes, depending on ligand preferences. TLR5, TLR4, and heterodimers like TLR2–TLR1 or TLR2–TLR6 recognize pathogenic components at the cell surface. TLR4 relocates to endosomes upon activation. Ligand binding triggers receptor dimerization and TIR domain interaction with adaptor proteins like TIRAP, MyD88, TRAM, and TRIF. TLR4 signaling shifts from MyD88 to TRIF post-endosomal translocation. MyD88 engages downstream signaling, forming the Myddosome with IRAK4 and IRAK1/2, activating TAK1, IKK, and NF-κB. TAK1 activates MAPKs (JNK, p38, ERK1/2), enhancing pro-inflammatory gene expression with NF-κB, CREB, and AP-1. TRIF recruits TRAF6, TRAF3, RIP1, TAK1, IKK, and MAPKs, leading to NF-κB activation. TRAF3 activates TBK1/IKKε, phosphorylating IRF3 for Type I IFN induction. TLRs thus orchestrate immune responses through diverse signaling cascades upon pathogen recognition [20,33].

TLR4 triggers both the MyD88-dependent and TRIF-dependent pathways, which are controlled by different molecules to initiate the necessary reactions. Maintaining a delicate balance between the production of inflammatory cytokines and type I IFN is essential in managing the growth of tumor cells and preventing autoimmune disorders. TRAF3 plays a crucial role in the signaling pathways of TLR4, being a key component of both the MyD88 and TRIF complexes. Within the MyD88 complex, the activation of TAK1 is triggered by the degradation of TRAF3. TRAF3 has a dual function, boosting the activation of the TRIF-dependent pathway while suppressing the MyD88-dependent pathway. In order to decrease inflammatory cytokine production and increase type I IFN production, the E3 ubiquitin ligase NRDP-1 binds with MyD88 and TBK1, ubiquitinates them, and promotes the breakdown of

MyD88. This, in turn, enhances the activation of TBK1 [19,195].

Upon activation by ligands, MyD88 facilitates the recruitment of IRAK-4 to TLRs via the interaction of their death domains. Phosphorylation of IRAK-1 and its interaction with TRAF6 leads to the activation of the IKK complex, which in turn activates MAPKs (JNK, p38 MAPK) and NF-κB [196]. Tollip and IRAK-M form interactions with IRAK-1, resulting in the inhibition of TLR-mediated signaling pathways [197]. ST2L, TRIAD3A, and SOCS1 block TIRAP-mediated downstream signaling, while RIP1 triggers TRAF6 signaling in a TRIF-dependent way. To govern TLR-mediated signaling pathways, adaptors with TIR domains like TIRAP, TRIF, and TRAM provide specificity for different TLR signaling cascades. MyD88-independent pathways are activated by TRIF and TRAF3, which bind IKKε/TBK1, phosphorylate IRF3, and express interferon-γ. By regulating TRAF3 degradation, TRAF3 promotes MyD88-dependent signaling and suppresses TRIF-dependent signaling, two types of signaling that are reliant on each other [198,199].

Together, these tightly orchestrated signaling events highlight how TLRs shape immune responses in periodontitis. A nuanced understanding of this network opens the door to targeted interventions aimed at correcting immune dysregulation and mitigating periodontal tissue destruction.

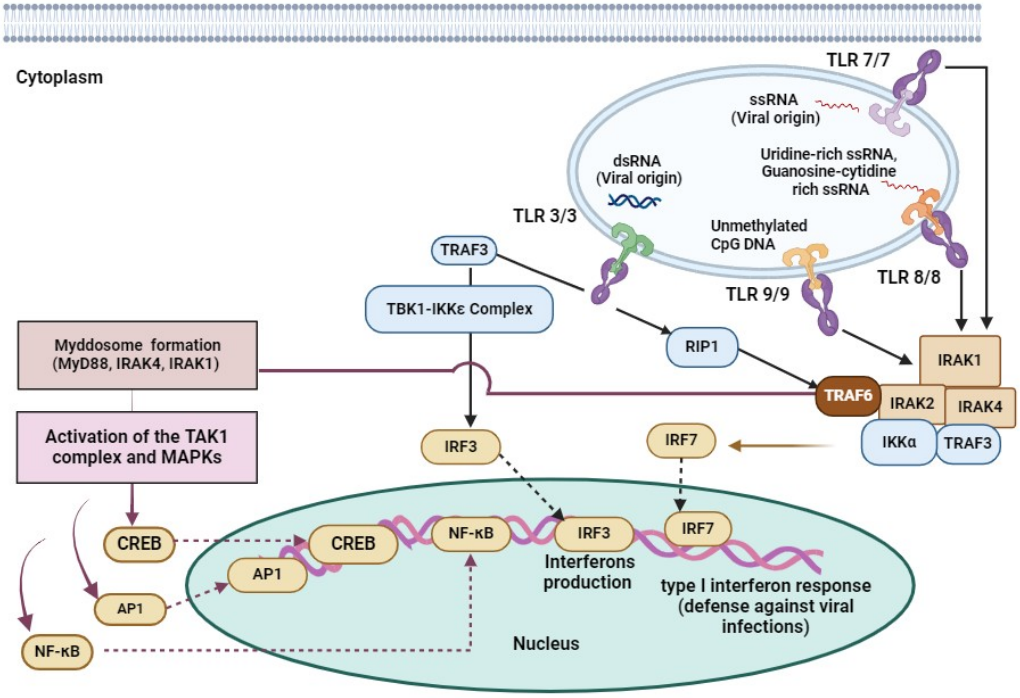

Figure 2. Endosomal TLR signaling pathways leading to inflammatory and antiviral responses.

Note: When endosomal TLRs are activated, MyD88 binds to their cytoplasmic domains, initiating signaling that leads to nuclear translocation of pro-inflammatory transcription factors. Upon TLR activation, IRAK proteins and TRAF6 are recruited, with IRAK-1 interacting with MyD88. TRAF6 activation can engage RIP1, activating TAK1 and IKK, subsequently leading to NF-κB and MAPK activation. TRIF facilitates TRAF3-mediated stimulation of TBK1 and IKKε, activating IRF3. TLR7, TLR8, and TLR9 in pDCs activate IRF7 via Myddosome, triggered by IRAK1 and IKKε, resulting in Type I IFN production [20,33].

4.1. Impact of Toll-like Receptor Signaling on Systemic Health

The impact of TLR signaling on systemic health is profound and multifaceted, affecting various physiological systems, including the immune, cardiovascular, respiratory, gastrointestinal, nervous, and reproductive systems. TLRs represent a class of proteins crucial to the innate immune system, recognizing structurally conserved molecules derived from microbes and initiating immune responses. Their broad influence underscores their significance in coordinating immune defense and influencing overall physiological homeostasis [200,201]. This exploration of TLR signaling and its influence on systemic health highlights its effects on reproductive health, as well as other critical bodily functions.

Cardiovascular health is particularly sensitive to TLR4 signaling. Activation in endothelial cells and macrophages promotes atherosclerosis by inducing inflammation and lipid accumulation. In contrast, TLR3 has shown protective

effects in myocardial injury models, illustrating the context-dependent roles of different TLRs [202–205].

In the respiratory system, TLRs defend against airborne pathogens, but excessive activation can lead to chronic conditions like asthma and chronic obstructive pulmonary disease [206]. TLR4, for instance, mediates responses to air pollution and allergens, contributing to airway inflammation and hyper-responsiveness [207].

Gastrointestinal (GI) homeostasis relies on balanced TLR signaling to maintain tolerance toward commensal microbes while defending against pathogens. Dysregulation here is linked to inflammatory bowel diseases like Crohn's disease and ulcerative colitis [208,209]. In the nervous system, TLR signaling is involved in neuroinflammation and neurodegeneration. TLRs on microglia detect damage and infection, leading to the production of neuroprotective factor [76, 210]. However, chronic activation contributes to neurological diseases like Alzheimer's disease, Parkinson's disease, and multiple sclerosis by perpetuating inflammatory responses and neuronal damage [211,212].

Reproductive health is also influenced by TLR signaling. In females, TLRs protect against sexually transmitted infections, but aberrant activation can lead to pelvic inflammatory disease, preterm labor, and preeclampsia [213]. In males, TLRs are involved in sperm maturation, influencing sperm quality [214], with dysregulation associated with conditions like prostatitis and reduced fertility [215].

Altogether, the role of TLRs in periodontitis extends far beyond oral immunity. Their ability to initiate and sustain both local and systemic inflammation positions them at the intersection of oral and systemic health. As such, modulating TLR activity holds promise not only for treating periodontitis but also for mitigating its broader health consequences. Continued exploration of TLR signaling pathways offers a gateway to more precise, targeted, and holistic therapeutic strategies.

The role of TLRs is multifaceted across different phases of disease, as depicted in **Table 3**. For example, in arthritis, TLR3 is associated with early inflammatory responses, while TLR7 contributes to chronic progression by sustaining inflammation [216–218]. Similarly, in Parkinson's disease, TLR3 and TLR2 are implicated in disease onset and progression, respectively, underscoring their potential as phase-specific therapeutic targets [219,220].

The diverse functions of TLRs across pathological contexts highlight their therapeutic relevance. In periodontitis, for instance, inhibiting TLR2 and TLR4 signaling can reduce inflammation while preserving essential antimicrobial defenses [221]. In autoimmune conditions such as systemic lupus erythematosus (SLE), TLR7 and TLR9 play central roles in modulating disease activity and therefore present promising targets for therapeutic intervention [222,223].

Overall, these findings underscore the distinct and disease-specific roles of TLRs, reinforcing the importance of developing targeted strategies that modulate TLR activity to alleviate inflammation and facilitate resolution in conditions such as inflammatory arthritis, neurodegenerative diseases, and autoimmune disorders.

Table 3. TLR involvement in disease onset, progression and resolution.

No	Disease	TLR	Phase	Role	Refs
1	Alzheimer's Disease	TLR2, TLR4	Onset	TLR4 activation has been linked to neuroinflammation and amyloid pathology in Alzheimer's.	Hajishengallis & Lambris [224], Walter et al. [225]
		TLR2, TLR4, TLR9	Progression	TLR2 mediates inflammatory responses in microglia associated with neuronal damage.	Hajishengallis & Lambris [224], Scholtzova et al. [226], Calvo-Rodríguez et al. [227]
		TLR2, TLR4, TLR9	Resolution	Targeting TLRs may alleviate neuroinflammation and improve cognitive functions.	Hajishengallis & Lambris [224], Wang et al. [228]
2	Arthritis	TLR3	Onset	TLR3 expression increases during the early onset phase of arthritis, indicating a stress-induced inflammatory response linked to synovial fibroblast activation.	Zhu et al. [216], Meng et al. [218]
		TLR2, TLR4, TLR7	Progression	Both TLR2 and TLR4 are critically involved in triggering and sustaining inflammatory responses in arthritis. TLR7 has been implicated in the maintenance of the disease, suggesting that enhanced TLR7 signaling contributes to chronic inflammatory states.	Alzabin et al. [217]
		TLR2, TLR4	Resolution	Therapeutic interventions targeting TLR2 and TLR4 pathways may promote the resolution of inflammation in arthritic patients by modulating the immune response.	Kay et al. [229]

Table 3. *Cont.*

No	Disease	TLR	Phase	Role	Refs
3	Autoimmunity	TLR7, TLR9	Onset	TLR7 senses RNA and TLR9 senses unmethylated CpG DNA, both critical for initiating autoimmune responses.	Heinz et al. [230], Odhams et al. [231]
		TLR2, TLR4	Progression	Chronic activation of these receptors fosters the perpetuation of autoimmune insults.	Caielli et al. [232], Ban et al. [233]
		TLR2	Resolution	Modulating TLR activity or signaling pathways could lead to decreased autoimmune manifestations.	Caielli et al. [232], McGarry et al. [234]
4	Atherosclerosis	TLR2, TLR4	Onset	TLR2 and TLR4 contribute to the inflammatory processes in atherogenesis by recognizing oxidized LDL.	Kalliolias et al. [235], Chávez-Sánchez et al. [236]
		TLR2, TLR4, TLR7	Progression	Chronic activation drives plaque growth and instability via sustained NF-κB activation, cytokine production, and recruitment of inflammatory cells. Promotes necrotic core formation and matrix degradation.	Kalliolias et al. [235], Schoneveld et al. [237], Shafeghat et al. [238]
		TLR2, TLR3, TLR4, TLR9	Resolution	Strategies that inhibit TLR signaling may reduce inflammation and promote plaque stabilization.	Kalliolias et al. [235], Cole et al. [239], Koulis et al. [240]
5	Chronic Periodontitis	TLR2, TLR4	Onset	In chronic periodontitis, TLR2 and TLR4 recognize oral pathogens and initiate inflammatory responses.	Rajendran et al. [241], Liao et al. [242]
		TLR2, TLR4, TLR9	Progression	TLR9 is involved in the progression of periodontal disease through its role in regulating immune cell activation.	Albuquerque-Souza et al. [99], Yılmaz et al. [243]
		TLR2, TLR3, TLR4, TLR9	Resolution	Inhibiting TLR-mediated effects may enhance healing and reduce tissue destruction.	Liao et al. [242], Zeng et al. [244]
6	Crohn's Disease	TLR4	Onset	TLR4 activation in the gut microbiota is implicated in the pathogenesis of Crohn's Disease.	Hajishengallis & Lambris [224], Kalliolias et al. [235]
		TLR9	Progression	TLR9 mediates immune activation in response to bacterial DNA, further contributing to localized inflammation.	Hajishengallis & Lambris [224]
		TLR9	Resolution	TLR9 signaling supports mucosal healing and epithelial repair. TLR9-deficient mice exhibit impaired wound healing and delayed recovery in DSS-induced colitis models.	Hajishengallis & Lambris [224], Rose et al. [245]
7	IgA Nephropathy	TLR4	Onset	Evidence suggests TLR4 is involved in the inflammatory response during the onset of IgA nephropathy, influencing disease exacerbation.	Coppo et al. [246], Ciferská et al. [247]
		TLR9	Progression	Specific TLR9 polymorphisms correlate with disease progression, indicating genetic influences on the disease course.	Ciferská et al. [247], Nakata et al. [248]
		TLR4, TLR7	Resolution	In the resolution phase of IgA nephropathy, TLR7 plays a critical role in modulating inflammation and promoting recovery, while specifically blocking TLR4 signaling may also facilitate improved renal health.	Zheng et al. [249], Zou et al. [250]
8	Inflammatory Bowel Disease (IBD)	TLR2, TLR4, TLR5	Onset	Recognition of lipoproteins, LPS, and flagellin by intestinal epithelial cells and lamina propria immune cells triggers innate responses, loss of barrier integrity, and recruitment of inflammatory cells that initiate colitis.	Hajishengallis & Lambris [224], El-Sayed et al. [251], Cario [252]
		TLR4, TLR2, TLR5, endosomal TLRs (TLR7/8/9)	Progression	Chronic/over-activation sustains NF-κB and type I IFN pathways, drives proinflammatory cytokine release (TNF, IL-1β, IL-6), promotes dysbiosis, epithelial damage, and adaptive immune activation that perpetuates disease. TLR5 (flagellin) dysregulation is linked to Crohn-type pathology.	Ren et al. [253], Feng et al. [254], Guo et al. [255]
		TLR2, TLR3, TLR9	Resolution	Inhibitors targeting TLR signaling pathways may help achieve remission.	Hajishengallis & Lambris [224], Schmitt et al. [256]
9	Parkinson's Disease	TLR2, TLR4	Onset	Activation by α-synuclein and neurotoxins triggers microglial inflammation, disrupting autophagy and accelerating α-syn aggregation and neuronal dysfunction.	Chung et al. [257]
		TLR4, TLR9	Progression	TLR4 deficiency worsens toxin-induced PD. TLR9 deletion protects in experimental models.	Adhikarla et al. [210], Maatouk et al. [258]
		TLR4	Resolution	Inhibiting TLR4 signaling can promote recovery from neuroinflammation in later stages of the disease.	Leventhal & Schröppel [259]

Table 3. *Cont.*

No	Disease	TLR	Phase	Role	Refs
10	Periodontitis	TLR2, TLR4	Onset	TLR2 and TLR4 are crucial in the initial immune response to periodontal pathogens, such as *P. gingivalis*, triggering inflammation.	El-Sayed et al. [90], Kim et al. [100]
		TLR9	Progression Resolution	Continuous activation of TLR9 in immune cell subsets leads to alveolar bone loss and exacerbates inflammation. Limited resource.	Kim et al. [100]
11	Rheumatoid Arthritis	TLR2, TLR3, TLR4	Onset	TLR4 activation is pivotal in recognizing endogenous danger signals in the joint, leading to the onset of rheumatoid arthritis.	Hajishengallis & Lambris [224], Kalliolias et al. [235], Brentano et al. [260]
		TLR2, TLR4	Progression	TLR2 plays a crucial role in sustaining synovial inflammation, contributing to disease progression. In animal models, TLR4 deficiency protects against severe arthritis via reduced Th17 responses.	Kalliolias et al. [235], Abdollahi-Roodsaz [261]
			Resolution	Limited direct evidence implicating any TLR in actively promoting the resolution of RA.	
12	Sepsis	TLR2, TLR4	Onset	TLR4 is vital for recognizing LPS, initiating the sepsis cascade through pro-inflammatory cytokine release.	Hajishengallis & Lambris [224], Kužnik et al. [262], Chen e. [263]
		TLR3, TLR5, TLR7, TLR9	Progression	During sepsis' progression, TLR signaling leads to persistent inflammation, contributing to organ dysfunction.	Kužnik et al. [262], Chen e. [263]
			Resolution	No TLR has been definitively linked to actively facilitating recovery.	
13	Systemic Lupus Erythematosus (SLE)	TLR7	Onset	TLR7 activation is critical in early disease manifestation by mediating antinuclear antibody production.	Tilstra et al. [264], Zhang et al. [265], Smith et al. [266]
		TLR7, TLR9	Progression	TLR7 exacerbates disease by promoting autoantibody production. Continuous stimulation of TLR9 is linked to the exacerbation of SLE and disease flares.	Zhu et al. [267], Gao et al. [268], Santiago-Raber et al. [269]
		TLR7/8, TLR9	Resolution	Targeting TLR7/8 activities may facilitate regulatory pathways necessary for the resolution phase in SLE. TLR9 polymorphisms correlate with lupus susceptibility in humans, with ethnic variations noted.	Wang et al. [270], Lee & Song [271]
14	Viral Infections	TLR3, TLR7/8, TLR9	Onset	pDC antiviral IFN via TLR7/9; influenza sensed via TLR7; DNA viruses via TLR9.	Heinz et al. [230], Yun et al. [272], Krug et al. [273]
		TLR2, TLR4, TLR7/9	Progression	Some viruses, engaging TLR2, induce MyD88/NF-κB inflammation. TLR4 is engaged by RSV F protein and airway inflammation. Exaggerated TLR7 signaling can drive immunopathology in susceptible settings.	Ma & He [274], Rallabhandi et al. [275], Saidoune et al. [276]
		TLR7, TLR9	Resolution	Therapeutically tuning TLR7/9 can modulate IFN and inflammation.	Kužnik et al. [262], Kader et al. [277]
15	Viral Myocarditis	TLR3	Onset	TLR3 recognizes viral double-stranded RNA, triggering innate immune responses crucial for controlling viral replication. TLR3 deficiency increases viral load and early damage.	Hajishengallis & Lambris [224], Abston et al. [278]
		TLR4	Progression	Upregulated TLR4 in the heart promotes NF-κB-driven cytokines and worsens myocardial inflammation and injury. Silencing or antagonizing TLR4 reduces disease severity in Coxsackievirus B3 models.	Zhao et al. [279], Zheng & Dong [280]
		TLR4 (inhibition); TLR3 (support)	Resolution	Improved outcomes with TLR4 inhibition; IFN-β protective in CVB3 myocarditis.	Kužnik et al. [262], Zhao et al. [279], Yajima & Knowlton [281]

5. Epigenetic Modifications and MicroRNA-Mediated Control of TLR Pathways

Epigenetic modifications play a key role in shaping miRNA expression profiles, which can significantly influence TLR signaling pathways. Epigenetic modifications such as DNA methylation and histone acetylation can either silence or activate genes, including those responsible for miRNA transcription. Hypermethylation can inhibit the expression of particular miRNAs, limiting the host's ability to modulate inflammatory responses to TLR activation. In conditions such as chronic inflammation or infection, altered epigenetic landscapes may contribute to dysregulated TLR signaling, ultimately exacerbating pathologies such as autoimmunity [282,283].

MicroRNAs (miRNAs) play a significant role in the regulation of TLR signaling pathways, modulating immune

responses across various conditions. Their involvement can enhance our understanding of immune dysregulation and may provide therapeutic targets for intervention. Certain miRNAs can directly interact with components of the TLR signaling pathway, modulating both the expression and function of TLRs. The miR-146a is a well-characterized negative regulator of TLR signaling; it targets key adaptor proteins such as IRAK1 and TRAF6, thereby dampening downstream NF-κB activation and limiting pro-inflammatory cytokine production. This regulatory mechanism is essential for maintaining immune homeostasis and preventing excessive or chronic immune activation, which is particularly relevant in autoimmune conditions such as SLE and RA. In SLE, the consensus from multiple studies is that miR-146a expression is generally downregulated or underexpressed [284]. In contrast to SLE, studies on RA consistently show that miR-146a is upregulated or overexpressed in patients. This is particularly noted in the inflamed synovial tissue, synovial fluid, and peripheral blood mononuclear cells [285]. Dysregulation or reduced expression of miR-146a has been associated with heightened inflammatory responses and disease severity in these disorders [284,286–288].

External factors such as diet, pollution, and stress can lead to epigenetic modifications that subsequently alter miRNA expression. For example, certain dietary components can induce DNA methylation changes, affecting the expression of miRNAs involved in TLR signaling pathways. This suggests that lifestyle choices may considerably influence an individual's immune response and susceptibility to diseases, making it essential to understand how these factors can be managed to promote better health outcomes [289].

miRNAs play a critical role in modulating the production of pro-inflammatory cytokines following TLR activation. These small non-coding RNAs act as fine-tuners of the innate immune response by either promoting or attenuating cytokine expression. For example, miR-155 is rapidly induced upon TLR stimulation and enhances the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, thereby amplifying the inflammatory response [287]. In contrast, miR-146a serves as a negative feedback regulator, attenuating excessive inflammation by targeting key TLR signaling intermediates and subsequently reducing cytokine levels such as IL-6 and TNF-α [290, 291]. This balance between pro- and anti-inflammatory miRNAs is essential for preventing chronic inflammation and immune-mediated tissue damage.

In IgA nephropathy (IgAN), a growing body of research highlights the potential of miRNAs as non-invasive biomarkers that reflect disease progression, severity, and even therapeutic response. Among these, miR-148a-3p, miR-425-3p, and miR-20a-5p have been found at elevated levels in patients with IgAN, suggesting a close association with immune dysregulation and renal injury characteristic of the disease [292,293]. These circulating miRNAs may serve as useful indicators of disease activity and could support more personalized monitoring approaches. Additionally, miR-204 has emerged as a promising predictive biomarker for IgAN progression. Lower expression levels of miR-204 in urinary samples have been linked to a higher risk of renal function decline, underscoring its potential role in risk stratification and early intervention strategies [294]. In chronic conditions such as IgA nephropathy, disturbances in miRNA expression driven by epigenetic alterations may lead to unregulated TLR signaling, resulting in persistent inflammation and tissue damage [295,296]. Understanding the epigenetic control of miRNAs presents a promising avenue for developing therapeutic strategies aimed at correcting dysregulated immune responses in diseases characterized by inappropriate TLR activation.

miRNAs regulate not only TLRs but also other PRRs, such as NLRs, thereby contributing to a broader regulatory network that shapes innate immune responses. A well-studied example is miR-223, which directly modulates the activation of the NLRP3 inflammasome involved in the maturation and secretion of pro-inflammatory cytokines such as IL-1β and IL-18. By targeting NLRP3 mRNA, miR-223 acts as a negative regulator of inflammasome activation, helping to maintain immune homeostasis and prevent excessive inflammation [297–299]. This regulatory role is especially relevant in renal diseases, including IgA nephropathy and diabetic nephropathy, where uncontrolled inflammasome activation contributes to chronic kidney injury. Reduced expression of miR-223 has been associated with enhanced NLRP3 activation, increased inflammatory cytokine production, and subsequent tissue damage in kidney tissues [300]. For example, research by Wang et al. elucidates the role of miR-223 in reducing IL-1β levels by targeting NLRP3 in human dental pulp fibroblasts, indicating a similar mechanism in other cell types [301]. Furthermore, the study by Tian et al. demonstrates how silencing of miR-223 results in enhanced expression of IL-1β, solidifying its role in controlling cytokine levels during inflammatory processes [302].

The interplay between epigenetic modifications, miRNA expression, and TLR signaling underscores the complexity of immune regulation in periodontitis, where environmental and lifestyle factors strongly influence disease

outcomes. By modulating receptor families such as TLRs and NLRs, miRNAs fine-tune innate immune responses, enhancing specificity, maintaining balance, and promoting resolution.

6. Therapeutic Implications and Future Perspectives

6.1. Targeting Toll-like Receptors as a Potential Therapeutic Approach

The recognition of TLRs as key modulators in the immune response to periodontopathic bacteria provides a promising strategy for therapeutic intervention in periodontitis. TLRs, particularly TLR2 and TLR4, are pivotal in detecting microbial components such as LPS and lipoproteins, which activate downstream inflammatory pathways. Therapeutic modulation of TLR pathways offers potential to selectively suppress pathological inflammation without compromising host defense [30,303]. Strategies under investigation target specific TLRs or their adaptor proteins, such as MyD88 and TRIF, which are summarized in **Table 4**.

Table 4. Potential therapeutic strategies targeting TLRs in the context of periodontitis.

Strategy	Target TLR	Mechanism of Action	Supporting Evidence	Refs
Small molecule inhibitors	TLR4	Block LPS-TLR4 interaction and downstream signaling	TAK-242 reduced cytokine levels and bone loss in murine periodontitis models	Hua et al. [304], Liu et al. [305]
Monoclonal antibodies	TLR2, TLR4	Neutralize receptor activation	Anti-TLR2 Ab inhibited inflammation in *P. gingivalis*-infected mice	Hajishengallis et al. [97], Clark et al. [306]
TRAM-Derived Decoy Peptides	TLR4	Interfere with TLR4 adaptor (TRAM) binding	Reduced proinflammatory response in LPS-stimulated macrophages	Piao et al. [307], Matsuguchi et al. [308]
siRNA/antisense oligonucleotides	TLR2, MyD88	Silence gene expression of TLRs or downstream adaptors	TLR2 siRNA decreased IL-1β production in human periodontal ligament cells	Hajishengallis et al. [309], Makkawi et al. [312]
Probiotic-derived TLR modulators	TLR2, TLR4	Competitive inhibition of pathogenic TLR ligands	*Lactobacillus* spp. reduced TLR4-mediated cytokine production *in vitro*	Finamore et al. [311], Kanmani et al. [312]

Peptide inhibitors targeting TLRs have shown significant promise in modulating immune responses, particularly in the context of inflammation and autoimmune diseases. Among the various peptides studied, specific examples highlight their mechanisms of action, strengths, and limitations. It has been reported that the effectiveness of peptides derived from the TRAM region, specifically TM4 and TM6, disrupts the assembly of TLR4 signaling complexes. These peptides inhibit the TIR: TIR interactions required for adaptor recruitment, effectively blocking MyD88- and TRIF-dependent cytokine production in LPS-stimulated macrophages. The study indicates that these decoy peptides can reduce pro-inflammatory cytokine levels, revealing their therapeutic potential against systemic inflammation [307,308].

One notable peptide is the viral inhibitory peptide (VIPER), derived from the vaccinia virus protein A46. This peptide has been demonstrated to inhibit TLR4 signaling by directly targeting the MyD88 adaptor-like and TRIF-related adaptor molecule, effectively blocking the downstream signaling that leads to pro-inflammatory cytokine production [313]. The specificity of VIPER for TLR4 makes it a compelling candidate for therapeutic applications; however, its efficacy *in vivo* and potential immunogenicity require thorough evaluation before clinical use.

Another important example is the TLR2-interfering peptide, known as the wild-type TIDM peptide, which selectively disrupts the interaction between TLR2 and its adaptor MyD88. This specific targeting allows it to inhibit TLR2-specific signaling pathways while sparing other TLR pathways, potentially reducing side effects associated with broad-spectrum TLR inhibition [314]. Although this peptide demonstrates significant promise in reducing inflammation related to Alzheimer's disease, challenges remain in optimizing its delivery and stability within biological systems.

Furthermore, the novel peptide TIP1 has garnered attention for its ability to inhibit multiple TLR signaling pathways, both MyD88-dependent and MyD88-independent, showcasing its utility in addressing broader inflammatory conditions caused by excessive TLR activation [315]. While the multi-functional capability of TIP1 presents

a strategic advantage, its potential for systemic effects could pose risks, necessitating a balance between therapeutic efficacy and safety.

Moreover, peptides such as Cecropin B, derived from insects, interact with TLR2 and TLR4. While they serve to activate immune pathways against pathogens, they also have the capacity to repress certain signaling pathways, suggesting a dual role in both antimicrobial activity and immune modulation [316]. The challenge with Cecropin B, similar to other antimicrobial peptides, is controlling its immune-modulatory effects, which can lead to unwanted inflammatory responses if not precisely regulated.

In addition, peptides derived from the Toll/IL-1 receptor (TIR) domain have been identified as cell-permeable decoy peptides, which can block TIR-TIR interactions essential for TLR signaling assembly. Recent reviews have addressed the therapeutic potential of decoy peptides in either enhancing or inhibiting TLR activity based on the disease context [317]. However, the efficacy and delivery mechanisms of these peptides in living organisms remain under extensive investigation.

Targeting TLRs represents a sophisticated approach to managing periodontitis, moving beyond broad-spectrum anti-inflammatory drugs. The challenge lies in developing highly specific modulators that can differentiate between beneficial and detrimental TLR activation, ensuring effective pathogen clearance without promoting excessive inflammation. Future research will focus on identifying optimal TLR targets, developing effective delivery mechanisms for these therapeutics, and conducting rigorous clinical trials to assess their safety and efficacy in human periodontitis patients. The ultimate goal is to offer more precise and personalized treatment options that can halt disease progression and promote long-term periodontal health.

6.2. Novel Strategies for Modulating Toll-like Receptor Signaling

While traditional strategies to control periodontitis have focused on mechanical plaque removal and antimicrobial treatments, recent advances in immunology offer new hope for managing this chronic inflammatory disease at its roots by targeting the signaling pathways. Emerging strategies to modulate TLR signaling are not limited to simply turning these pathways "off". Instead, researchers are developing more precise and flexible approaches that either enhance or suppress TLR responses depending on the clinical need. For instance, TLR agonists are being explored as vaccine adjuvants, where they can strengthen the immune system's ability to recognize and respond to microbial invaders. Agonists such as CpG oligodeoxynucleotides (TLR9 ligands) or Pam3CSK4 (TLR2 agonist) have already shown success in boosting mucosal immunity and may eventually be adapted for oral applications against periodontopathic pathogens [309,318–320].

On the other hand, TLR antagonists hold promise for cases where the immune system goes into overdrive, contributing to the chronic inflammation seen in periodontitis. Unlike broad-spectrum anti-inflammatory drugs, these agents aim to selectively block hyperactive TLR pathways, such as TLR2 or TLR4, that are directly implicated in driving destructive cytokine responses and tissue breakdown. Several natural and synthetic TLR antagonists, including Eritoran, TAK-242, and curcumin, have demonstrated anti-inflammatory effects in preclinical studies [321–323].

One of the most exciting areas of innovation lies in gene-silencing technologies. siRNA, antisense oligonucleotides, and even CRISPR-based systems are being investigated to selectively downregulate genes encoding TLRs or their adaptor molecules like MyD88. This approach allows for highly specific immune modulation, reducing inflammation without broadly suppressing host defenses. For example, TLR2-targeted siRNA has been shown to reduce IL-1β production in human periodontal ligament cells stimulated with *P. gingivalis* LPS, suggesting its potential to limit inflammation at a cellular level [324,325].

In parallel, attention has turned to the oral microbiome, a key modulator of TLR activity. Dysbiosis can promote inappropriate TLR activation, leading to chronic inflammation. This insight has spurred interest in probiotic and postbiotic therapies, which aim to restore microbial harmony and, in turn, rebalance TLR-mediated immune responses. Certain strains of *Lactobacillus* sp., for instance, have been shown to suppress TLR4-driven cytokine production, offering a non-invasive and natural means to modulate host immunity [326,327].

Additionally, advances in nanotechnology are helping overcome challenges in delivering these targeted therapies to periodontal tissues. Nanoparticle-based delivery systems, including liposomes and polymer-based carriers, can improve the precision and stability of TLR modulators, ensuring they reach inflamed sites with minimal systemic exposure. This is especially beneficial in a localized disease like periodontitis, where topical delivery may reduce side effects and enhance efficacy [328,329].

6.3. Challenges and Future Direction in Toll-like Receptor Research in Periodontitis

TLRs remain compelling therapeutic targets in periodontitis due to their central role in immune regulation. However, their intricate signaling networks, interactions with a diverse and adaptable microbiota, and sensitivity to environmental and genetic influences pose substantial challenges. TLRs initiate diverse, sometimes overlapping, signaling cascades that complicate the delineation of their specific functions in periodontal disease [330,331]. For instance, TLR2 and TLR4 can trigger both pro-inflammatory and anti-inflammatory pathways depending on the surrounding cytokine milieu and microbial composition, creating ambiguity in functional interpretation, particularly in therapeutic contexts. A more refined, context-specific understanding of TLR signaling is therefore critical for clarifying their role in disease progression and guiding targeted interventions.

The polymicrobial nature of the periodontal pocket presents another layer of complexity. TLRs interact with a wide array of microorganisms, including keystone pathogens like *P. gingivalis*, which can manipulate TLR signaling to evade immune responses and promote a dysbiotic microbial shift [21,224,331]. This dynamic underscores the paradoxical role of TLRs: while essential for host defense, they can also be exploited to sustain chronic inflammation. Consequently, TLR function must be examined within the ecological context of the oral microbiome.

Environmental and systemic factors further influence TLR activity. Smoking, for example, has been shown to alter TLR expression in gingival tissues, with significant differences in TLR2 and TLR4 levels between smokers and non-smokers with periodontitis [332]. Such variability introduces confounding factors in evaluating TLR-based therapies across patient populations. Genetic background also shapes TLR responsiveness; specific single-nucleotide polymorphisms in TLR genes are linked to differential susceptibility to periodontitis and variable immune reactivity [333]. Additionally, epigenetic modifications such as DNA methylation and histone changes further regulate TLR gene expression and function. These inter-individual differences necessitate a personalized medicine approach to TLR-based therapies, taking into account the genetic and epigenetic context of each patient. Future research priorities should include elucidating the context-dependent mechanisms by which TLRs modulate periodontal disease onset and progression, particularly in relation to diverse microbial communities [330,334].

A critical area of development involves identifying specific TLR ligands involved in periodontal disease and deciphering the crosstalk between TLRs and other immune receptors, such as NOD-like receptors. Understanding these interactions may enable the design of more precise therapeutic strategies that modulate inflammation without compromising innate immune defense. Among the promising therapeutic innovations are TLR-derived decoy peptides, such as TLR4 inhibitors that show potential in regulating excessive inflammatory responses [330,335]. Furthermore, advances in nanotechnology and multifunctional drug delivery systems are opening new avenues for the targeted delivery of TLR-modulating agents directly to periodontal tissues, offering enhanced efficacy and reduced systemic side effects [316,336].

Parallel efforts should investigate the genetic and epigenetic modulators of TLR signaling in diverse populations to enable precision-based periodontal care [313,314]. Addressing the complexity and redundancy of TLR signaling, as well as the translational gap between preclinical and clinical outcomes, will require interdisciplinary collaboration, advanced molecular tools, and innovative therapeutic platforms.

Finally, given the established associations between periodontitis and systemic inflammatory comorbidities such as diabetes and cardiovascular disease, research should also explore the broader implications of TLR modulation in systemic health [315,316]. Collectively, these future directions highlight the potential for translational breakthroughs in periodontal research and underscore the need for a holistic understanding of immune regulation within and beyond the periodontium.

7. Conclusion

TLRs are central to the immune system's recognition of periodontal pathogens, initiating protective responses but also driving chronic inflammation and tissue destruction when overactivated. Recent advances in decoding TLR signaling have spurred interest in targeted interventions—ranging from small molecules and peptides to RNA-based therapies and probiotics—that aim to modulate immune activity without compromising host defense. However, critical gaps remain, including a clearer understanding of how TLR expression varies across periodontal cell types and disease stages, and how miRNAs fine-tune these pathways. Unraveling these mechanisms is particularly important given that TLR-driven inflammation not only fuels periodontitis but is also linked to systemic conditions

such as cardiovascular disease, diabetes, and adverse pregnancy outcomes. In summary, TLRs sit at the intersection of microbial detection, immune response, and inflammation in periodontitis. By addressing the current knowledge gaps, particularly in TLR expression patterns and miRNA regulation, researchers can pave the way toward more precise, effective, and holistic approaches to managing periodontal and systemic health.

Author Contributions

Conceptualization, S.D. and F.F.L.; writing—original draft preparation, F.F.L., S.H.T., P.S., and S.D.; writing—review and editing, S.D. and F.F.L. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the Fundamental Research Grant Scheme, Ministry of Higher Education, Malaysia under FRGS/1/2019/SKK08/MAHSA/03/2.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest. The English language of the article was improved with ChatGPT and Gemini AI. Upon generating draft language, the author reviewed, edited, and revised the language to their liking and takes ultimate responsibility for the content of this publication.

References

1. Bhuyan, R.; Bhuyan, S.K.; Mohanty, J.N.; et al. Periodontitis and Its Inflammatory Changes Linked to Various Systemic Diseases: A Review of Its Underlying Mechanisms. *Biomedicines* **2022**, *10*, 2659.
2. Paul, O.; Arora, P.; Mayer, M.; et al. Inflammation in Periodontal Disease: Possible Link to Vascular Disease. *Front. Physiol.* **2021**, *11*, 609614.
3. Eke, P.I.; Dye, B.; Wei, L.; et al. Prevalence of Periodontitis in Adults in the United States: 2009 and 2010. *J. Dent. Res.* **2012**, *91*, 914–920.
4. Martínez-García, M.; Hernández-Lemus, E. Periodontal Inflammation and Systemic Diseases: An Overview. *Front. Physiol.* **2021**, *12*, 709438.
5. Balta, M.G.; Loos, B.G.; Nicu, E.A. Emerging Concepts in the Resolution of Periodontal Inflammation: A Role for Resolvin E1. *Front. Immunol.* **2017**, *8*, 1682.
6. Ray, R.R. Periodontitis: An Oral Disease with Severe Consequences. *Appl. Biochem. Biotechnol.* **2023**, *195*, 17–32.
7. Noor, S.; Gasmi, A. Porphyromonas Gingivalis in the Development of Periodontitis: Impact on Dysbiosis and Inflammation. *Arch. Razi Inst.* **2022**, *77*, 1539–1551.
8. Hoare, A.; Soto, C.; Rojas-Celis, V.; et al. Chronic Inflammation as a Link Between Periodontitis and Carcinogenesis. *Mediators Inflamm.* **2019**, *2019*, 1029857.
9. Abusleme, L.; Dupuy, A.K.; Dutzan, N.; et al. The Subgingival Microbiome in Health and Periodontitis and Its Relationship with Community Biomass and Inflammation. *ISME J.* **2013**, *7*, 1016–1025.
10. Darveau, R.P. Periodontitis: A Polymicrobial Disruption of Host Homeostasis. *Nat. Rev. Microbiol.* **2010**, *8*, 481–490.

11. Bassani, B.; Cucchiara, M.; Butera, A.; et al. Neutrophils' Contribution to Periodontitis and Periodontitis-Associated Cardiovascular Diseases. *Int. J. Mol. Sci.* **2023**, *24*, 15370.
12. Fox, S.; Leitch, A.E.; Duffin, R.; et al. Neutrophil Apoptosis: Relevance to the Innate Immune Response and Inflammatory Disease. *J. Innate Immun.* **2010**, *2*, 216–227.
13. Wallet, S.M.; Puri, V.; Gibson, F.C. Linkage of Infection to Adverse Systemic Complications: Periodontal Disease, Toll-Like Receptors, and Other Pattern Recognition Systems. *Vaccines* **2018**, *6*, 21.
14. Takeuchi, O.; Akira, S. Pattern Recognition Receptors and Inflammation. *Cell* **2010**, *140*, 805–820.
15. Akira, S.; Uematsu, S.; Takeuchi, O. Pathogen Recognition and Innate Immunity. *Cell* **2006**, *124*, 783–801.
16. Cai, X.; Chiu, Y.H.; Chen, Z.J. The cGAS-cGAMP-STING Pathway of Cytosolic DNA Sensing and Signaling. *Mol. Cell* **2014**, *54*, 289–296.
17. Iwasaki, A.; Medzhitov, R. Toll-Like Receptor Control of the Adaptive Immune Responses. *Nat. Immunol.* **2004**, *5*, 987–995.
18. Hayden, M.S.; Ghosh, S. NF-κB in Immunobiology. *Cell Res.* **2011**, *21*, 223–244.
19. Kawasaki, T.; Kawai, T. Toll-Like Receptor Signaling Pathways. *Front. Immunol.* **2014**, *5*, 461.
20. Duan, T.; Du, Y.; Xing, C.; et al. Toll-Like Receptor Signaling and Its Role in Cell-Mediated Immunity. *Front. Immunol.* **2022**, *13*, 812774.
21. Hajishengallis, G.; Darveau, R.P.; Curtis, M.A. The Keystone-Pathogen Hypothesis. *Nat. Rev. Microbiol.* **2012**, *10*, 717–725.
22. Shin, H.; Zhang, Y.; Jagannathan, M.; et al. B Cells from Periodontal Disease Patients Express Surface Toll-Like Receptor 4. *J. Leukoc. Biol.* **2009**, *85*, 648–655.
23. Taubman, M.A.; Valverde, P.; Han, X.; et al. Immune Response: The Key to Bone Resorption in Periodontal Disease. *J. Periodontol.* **2005**, *76*, 2033–2041.
24. Scapini, P.; Cassatella, M.A. Social Networking of Human Neutrophils within the Immune System. *Blood* **2014**, *124*, 710–719.
25. Pillay, J.; Kamp, V.M.; Van Hoffen, E.; et al. A Subset of Neutrophils in Human Systemic Inflammation Inhibits T Cell Responses through Mac-1. *J. Clin. Invest.* **2012**, *122*, 327–336.
26. Puga, I.; Cols, M.; Barra, C.M.; et al. B Cell–Helper Neutrophils Stimulate the Diversification and Production of Immunoglobulin in the Marginal Zone of the Spleen. *Nat. Immunol.* **2012**, *13*, 170–180.
27. Camous, L.; Roumenina, L.; Bigot, S.; et al. Complement Alternative Pathway Acts as a Positive Feedback Amplification of Neutrophil Activation. *Blood* **2011**, *117*, 1340–1349.
28. Dababneh, R.; Al-Wahadneh, A.M.; Hamadneh, S.; et al. Periodontal Manifestation of Leukocyte Adhesion Deficiency Type I. *J. Periodontol.* **2008**, *79*, 764–768.
29. Moutsopoulos, N.M.; Konkel, J.; Sarmadi, M.; et al. Defective Neutrophil Recruitment in Leukocyte Adhesion Deficiency Type I Disease Causes Local IL-17–Driven Inflammatory Bone Loss. *Sci. Transl. Med.* **2014**, *6*, 229ra40.
30. Gu, Y.; Han, X. Toll-Like Receptor Signaling and Immune Regulatory Lymphocytes in Periodontal Disease. *Int. J. Mol. Sci.* **2020**, *21*, 3329.
31. Yin, L.; Li, X.; Hou, J. Macrophages in Periodontitis: A Dynamic Shift between Tissue Destruction and Repair. *Jpn. Dent. Sci. Rev.* **2022**, *58*, 336–347.
32. Li, D.; Wu, M. Pattern Recognition Receptors in Health and Diseases. *Signal Transduct. Target. Ther.* **2021**, *6*, 291.
33. El-Zayat, S.R.; Sibaii, H.; Mannaa, F.A. Toll-Like Receptors Activation, Signaling, and Targeting: An Overview. *Bull. Natl. Res. Cent.* **2019**, *43*, 187.
34. Kawai, T.; Akira, S. The Roles of TLRs, RLRs and NLRs in Pathogen Recognition. *Int. Immunol.* **2009**, *21*, 317–337.
35. Zhang, G.; Ghosh, S. Toll-Like Receptor-Mediated NF-κB Activation: A Phylogenetically Conserved Paradigm in Innate Immunity. *J. Clin. Invest.* **2001**, *107*, 13–19.
36. Sitamahalakshmi, K.; Krishnakumar, G. Toll-Like Receptors in Periodontal Health and Disease. *Int. J. Appl. Dent. Sci.* **2022**, *84*, 148–157.
37. Mielcarska, M.B.; Bossowska-Nowicka, M.; Toka, F.N. Cell Surface Expression of Endosomal Toll-Like Receptors—A Necessity or a Superfluous Duplication? *Front. Immunol.* **2021**, *11*, 620972.
38. Kim, Y.M.; Brinkmann, M.M.; Paquet, M.E.; et al. UNC93B1 Delivers Nucleotide-Sensing Toll-Like Receptors to Endolysosomes. *Nature* **2008**, *452*, 234–238.
39. Kang, J.Y.; Lee, J.O. Structural Biology of the Toll-Like Receptor Family. *Annu. Rev. Biochem.* **2011**, *80*, 917–941.

40. Areal, H.; Abrantes, J.; Esteves, P.J. Signatures of Positive Selection in Toll-Like Receptor (TLR) Genes in Mammals. *BMC Evol. Biol.* **2011**, *11*, 368.
41. Wolff, H.; Anderson, D.J. Immunohistologic Characterization and Quantitation of Leukocyte Subpopulations in Human Semen. *Fertil. Steril.* **1988**, *49*, 497–504.
42. Sameer, A.S.; Nissar, S. Toll-Like Receptors (TLRs): Structure, Functions, Signaling, and Role of Their Polymorphisms in Colorectal Cancer Susceptibility. *Biomed. Res. Int.* **2021**, *2021*, 1–10.
43. Fuchsberger, M.; Hochrein, H.; O'Keeffe, M. Activation of Plasmacytoid Dendritic Cells. *Immunol. Cell Biol.* **2005**, *83*, 571–577.
44. Honda, K.; Yanai, H.; Mizutani, T.; et al. Role of a Transductional-Transcriptional Processor Complex Involving MyD88 and IRF-7 in Toll-Like Receptor Signaling. *Proc. Natl. Acad. Sci.* **2004**, *101*, 15416–15421.
45. Mbongue, J.; Nicholas, D.; Firek, A.; et al. The Role of Dendritic Cells in Tissue-Specific Autoimmunity. *J. Immunol. Res.* **2014**, *2014*, 857143.
46. Mnich, S.J.; Blanner, P.M.; Hu, L.G.; et al. Critical Role for Apoptosis Signal-Regulating Kinase 1 in the Development of Inflammatory K/BxN Serum-Induced Arthritis. *Int. Immunopharmacol.* **2010**, *10*, 1170–1176.
47. Roquilly, A.; McWilliam, H.E.; Jacqueline, C.; et al. Local Modulation of Antigen-Presenting Cell Development after Resolution of Pneumonia Induces Long-Term Susceptibility to Secondary Infections. *Immunity* **2017**, *47*, 135–147.
48. Hochrein, H.; O'Keeffe, M.; Wagner, H. Human and Mouse Plasmacytoid Dendritic Cells. *Hum. Immunol.* **2002**, *63*, 1103–1110.
49. Born, W.K.; Reardon, C.L.; O'Brien, R.L. The Function of γδ T Cells in Innate Immunity. *Curr. Opin. Immunol.* **2006**, *18*, 31–38.
50. Galley, H.F.; Lowes, D.A.; Thompson, K.; et al. Characterisation of Gamma Delta (γδ) T Cell Populations in Patients with Sepsis. *Cell Biol. Int.* **2015**, *39*, 210–216.
51. Wesch, D.; Peters, C.; Oberg, H.H.; et al. Modulation of γδ T Cell Responses by TLR Ligands. *Cell. Mol. Life Sci.* **2011**, *68*, 2357–2370.
52. Wesch, D.; Beetz, S.; Oberg, H.H.; et al. Direct Costimulatory Effect of TLR3 Ligand Poly(I:C) on Human γδ T Lymphocytes. *J. Immunol.* **2006**, *176*, 1348–1354.
53. Pietschmann, K.; Beetz, S.; Welte, S.; et al. Toll-Like Receptor Expression and Function in Subsets of Human γδ T Lymphocytes. *Scand. J. Immunol.* **2009**, *70*, 245–255.
54. Deetz, C.O.; Hebbeler, A.M.; Propp, N.A.; et al. Gamma Interferon Secretion by Human Vγ2Vδ2 T Cells after Stimulation with Antibody against the T-Cell Receptor plus the Toll-Like Receptor 2 Agonist Pam3Cys. *Infect. Immun.* **2006**, *74*, 4505–4511.
55. Hedges, J.F.; Lubick, K.J.; Jutila, M.A. Gamma Delta T Cells Respond Directly to Pathogen-Associated Molecular Patterns. *J. Immunol.* **2005**, *174*, 6045–6053.
56. Hotchkiss, R.S.; Osmon, S.B.; Chang, K.C.; et al. Accelerated Lymphocyte Death in Sepsis Occurs by Both the Death Receptor and Mitochondrial Pathways. *J. Immunol.* **2005**, *174*, 5110–5118.
57. Cao, C.; Ma, T.; Chai, Y.F.; et al. The Role of Regulatory T Cells in Immune Dysfunction during Sepsis. *World J. Emerg. Med.* **2015**, *6*, 5–9.
58. Taylor, A.L.; Llewelyn, M.J. Superantigen-Induced Proliferation of Human $CD4^+$ $CD25^-$ T Cells Is Followed by a Switch to a Functional Regulatory Phenotype. *J. Immunol.* **2010**, *185*, 6591–6598.
59. Venet, F.; Pachot, A.; Debard, A.L.; et al. Increased Percentage of $CD4^+$ $CD25^+$ Regulatory T Cells during Septic Shock Is Due to the Decrease of $CD4^+$ $CD25^-$ Lymphocytes. *Crit. Care Med.* **2004**, *32*, 2329–2331.
60. Venet, F.; Pachot, A.; Debard, A.L.; et al. Human $CD4^+$ $CD25^+$ Regulatory T Lymphocytes Inhibit Lipopolysaccharide-Induced Monocyte Survival through a Fas/Fas Ligand-Dependent Mechanism. *J. Immunol.* **2006**, *177*, 6540–6547.
61. Bekeredjian-Ding, I.; Jego, G. Toll-Like Receptors–Sentries in the B-Cell Response. *Immunology* **2009**, *128*, 311–323.
62. Ruprecht, C.R.; Lanzavecchia, A. Toll-Like Receptor Stimulation as a Third Signal Required for Activation of Human Naive B Cells. *Eur. J. Immunol.* **2006**, *36*, 810–816.
63. Buchta, C.M.; Bishop, G.A. TRAF5 Negatively Regulates TLR Signaling in B Lymphocytes. *J. Immunol.* **2014**, *192*, 145–150.
64. Ray, A.; Dittel, B.N. Mechanisms of Regulatory B Cell Function in Autoimmune and Inflammatory Diseases beyond IL-10. *J. Clin. Med.* **2017**, *6*, 12.
65. Zakeri, A.; Russo, M. Dual Role of Toll-Like Receptors in Human and Experimental Asthma Models. *Front. Immunol.* **2018**, *9*, 1027.

66. Supajatura, V.; Ushio, H.; Nakao, A.; et al. Differential Responses of Mast Cell Toll-Like Receptors 2 and 4 in Allergy and Innate Immunity. *J. Clin. Invest.* **2002**, *109*, 1351–1359.
67. Varadaradjalou, S.; Feger, F.; Thieblemont, N.; et al. Toll-Like Receptor 2 (TLR2) and TLR4 Differentially Activate Human Mast Cells. *Eur. J. Immunol.* **2003**, *33*, 899–906.
68. Keck, S.; Müller, I.; Fejer, G.; et al. Absence of TRIF Signaling in Lipopolysaccharide-Stimulated Murine Mast Cells. *J. Immunol.* **2011**, *186*, 5478–5488.
69. Kagan, J.C.; Su, T.; Horng, T.; et al. TRAM Couples Endocytosis of Toll-Like Receptor 4 to the Induction of Interferon-β. *Nat. Immunol.* **2008**, *9*, 361–368.
70. Kagan, J.C. Signaling Organelles of the Innate Immune System. *Cell* **2012**, *151*, 1168–1178.
71. Dietrich, N.; Rohde, M.; Geffers, R.; et al. Mast Cells Elicit Proinflammatory but Not Type I Interferon Responses upon Activation of TLRs by Bacteria. *Proc. Natl. Acad. Sci.* **2010**, *107*, 8748–8753.
72. McClure, R.; Massari, P. TLR-Dependent Human Mucosal Epithelial Cell Responses to Microbial Pathogens. *Front. Immunol.* **2014**, *5*, 386.
73. Yu, F.S.; Hazlett, L.D. Toll-Like Receptors and the Eye. *Invest. Ophthalmol. Vis. Sci.* **2006**, *47*, 1255–1263.
74. Wilhelmsen, K.; Mesa, K.R.; Lucero, J.; et al. ERK5 Protein Promotes, Whereas MEK1 Protein Differentially Regulates, the Toll-Like Receptor 2 Protein-Dependent Activation of Human Endothelial Cells and Monocytes. *J. Biol. Chem.* **2012**, *287*, 26478–26494.
75. Wong, E.; Xu, F.; Joffre, J.; et al. ERK1/2 Has Divergent Roles in LPS-Induced Microvascular Endothelial Cell Cytokine Production and Permeability. *Shock* **2021**, *55*, 349–356.
76. Li, L.; Acioglu, C.; Heary, R.F.; et al. Role of Astroglial Toll-Like Receptors (TLRs) in Central Nervous System Infections, Injury and Neurodegenerative Diseases. *Brain Behav. Immun.* **2021**, *91*, 740–755.
77. Bsibsi, M.; Ravid, R.; Gveric, D.; et al. Broad Expression of Toll-Like Receptors in the Human Central Nervous System. *J. Neuropathol. Exp. Neurol.* **2002**, *61*, 1013–1021.
78. Olson, J.K.; Miller, S.D. Microglia Initiate Central Nervous System Innate and Adaptive Immune Responses through Multiple TLRs. *J. Immunol.* **2004**, *173*, 3916–3924.
79. Farina, C.; Aloisi, F.; Meinl, E. Astrocytes Are Active Players in Cerebral Innate Immunity. *Trends Immunol.* **2007**, *28*, 138–145.
80. Farina, C.; Krumbholz, M.; Giese, T.; et al. Preferential Expression and Function of Toll-Like Receptor 3 in Human Astrocytes. *J. Neuroimmunol.* **2005**, *159*, 12–19.
81. Xie, L.; Chen, J.; Hu, H.; et al. Engineered M2 Macrophage-Derived Extracellular Vesicles with Platelet Membrane Fusion for Targeted Therapy of Atherosclerosis. *Bioact. Mater.* **2024**, *35*, 447–460.
82. Li, J.L.; Zarbock, A.; Hidalgo, A. Platelets as Autonomous Drones for Hemostatic and Immune Surveillance. *J. Exp. Med.* **2017**, *214*, 2193–2204.
83. Blair, P.; Rex, S.; Vitseva, O.; et al. Stimulation of Toll-Like Receptor 2 in Human Platelets Induces a Thromboinflammatory Response through Activation of Phosphoinositide 3-Kinase. *Circ. Res.* **2009**, *104*, 346–354.
84. Cognasse, F.; Nguyen, K.A.; Damien, P.; et al. The Inflammatory Role of Platelets via Their TLRs and Siglec Receptors. *Front. Immunol.* **2015**, *6*, 83.
85. Ebersole, J.L.; Kirakodu, S.; Novak, M.J.; et al. Comparative Analysis of Expression of Microbial Sensing Molecules in Mucosal Tissues with Periodontal Disease. *Immunobiology* **2019**, *224*, 196–206.
86. Seubbuk, S.; Surarit, R.; Stephens, D.; et al. TLR2 and TLR4 Differentially Regulate the Osteogenic Capacity of Human Periodontal Ligament Fibroblasts. *J. Int. Acad. Periodontol.* **2021**, *23*, 3–10.
87. Takahashi, N.; Sulijaya, B.; Yamada-Hara, M.; et al. Gingival Epithelial Barrier: Regulation by Beneficial and Harmful Microbes. *Tissue Barriers* **2019**, *7*, e1651158.
88. Karlis, G.D.; Schöningh, E.; Jansen, I.D.C.; et al. Chronic Exposure of Gingival Fibroblasts to TLR2 or TLR4 Agonist Inhibits Osteoclastogenesis but Does Not Affect Osteogenesis. *Front. Immunol.* **2020**, *11*, 1693.
89. Wielento, A.; Łagosz-Ćwik, K.; Potempa, J.; et al. The Role of Gingival Fibroblasts in the Pathogenesis of Periodontitis. *J. Dent. Res.* **2023**, *102*, 489–496.
90. El-Sayed, K.M.F.; Klingebiel, P.; Dörfer, C.E. Toll-Like Receptor Expression Profile of Human Dental Pulp Stem/Progenitor Cells. *J. Endod.* **2016**, *42*, 413–417.
91. Fawzy-El-Sayed, K.; Mekhemar, M.; Adam-Klages, S.; et al. TLR Expression Profile of Human Gingival Margin-Derived Stem Progenitor Cells. *Med. Oral Patol. Oral Cir. Bucal* **2016**, *21*, e30.
92. El-Sayed, K.M.F.; Boeckler, J.; Dörfer, C.E. TLR Expression Profile of Human Alveolar Bone Proper-Derived Stem/Progenitor Cells and Osteoblasts. *J. Craniomaxillofac. Surg.* **2017**, *45*, 2054–2060.
93. Fehrmann, C.; Dörfer, C.E.; El-Sayed, K.M.F. Toll-Like Receptor Expression Profile of Human Stem/Progenitor Cells from the Apical Papilla. *J. Endod.* **2020**, *46*, 1623–1630.

94. Zymovets, V.; Rakhimova, O.; Wadelius, P.; et al. Exploring the Impact of Oral Bacteria Remnants on Stem Cells from the Apical Papilla: Mineralization Potential and Inflammatory Response. *Front. Cell. Infect. Microbiol.* **2023**, *13*, 1257433.
95. Siqueira, J.; Rôças, I.N.; Ricucci, D.; et al. Causes and Management of Post-Treatment Apical Periodontitis. *Br. Dent. J.* **2014**, *216*, 305–312.
96. Sun, Y.; Guo, Q.M.; Liu, D.L.; et al. In Vivo Expression of Toll-Like Receptor 2, Toll-Like Receptor 4, CSF2 and LY64 in Chinese Chronic Periodontitis Patients. *Oral Dis.* **2010**, *16*, 343–350.
97. Hajishengallis, G.; Sojar, H.; Genco, R.J.; et al. Intracellular Signaling and Cytokine Induction upon Interactions of Porphyromonas gingivalis Fimbriae with Pattern-Recognition Receptors. *Immunol. Investig.* **2004**, *33*, 157–172.
98. Wara-Aswapati, N.; Chayasadom, A.; Surarit, R.; et al. Induction of Toll-Like Receptor Expression by Porphyromonas gingivalis. *J. Periodontol.* **2013**, *84*, 1010–1018.
99. Albuquerque-Souza, E.; Crump, K.; Rattanaprukskul, K.; et al. TLR9 Mediates Periodontal Aging by Fostering Senescence and Inflammaging. *J. Dent. Res.* **2022**, *101*, 1628–1636.
100. Kim, P.D.; Xia-Juan, X.; Crump, K.E.; et al. Toll-Like Receptor 9-Mediated Inflammation Triggers Alveolar Bone Loss in Experimental Murine Periodontitis. *Infect. Immun.* **2015**, *83*, 2992–3002.
101. Frank, S.; Copanaki, E.; Burbach, G.J.; et al. Differential Regulation of Toll-Like Receptor mRNAs in Amyloid Plaque-Associated Brain Tissue of Aged APP23 Transgenic Mice. *Neurosci. Lett.* **2009**, *453*, 41–44.
102. Lyu, A.K.; Zhu, S.Y.; Chen, J.L.; et al. Inhibition of TLR9 Attenuates Skeletal Muscle Fibrosis in Aged Sarcopenic Mice via the p53/SIRT1 Pathway. *Exp. Gerontol.* **2019**, *122*, 25–33.
103. Sato, Y.; Tansho-Nagakawa, S.; Ubagai, T.; et al. Analysis of Immune Responses in Acinetobacter baumannii-Infected Klotho Knockout Mice: A Mouse Model of Acinetobacter baumannii Infection in Aged Hosts. *Front. Immunol.* **2020**, *11*, 601614.
104. Beklen, A.; Hukkanen, M.; Richardson, R.; et al. Immunohistochemical Localization of Toll-Like Receptors 1–10 in Periodontitis. *Oral Microbiol. Immunol.* **2008**, *23*, 425–431.
105. Janssens, S.; Beyaert, R. Role of Toll-Like Receptors in Pathogen Recognition. *Clin. Microbiol. Rev.* **2003**, *16*, 637–646.
106. Han, H.; Lian, P.; Chen, H.; et al. The Assessment of TLR1 Gene Polymorphism Association with the Risk of Allergic Rhinitis in the Chinese Han Population from Northern China. *J. Asthma Allergy* **2023**, *16*, 979–986.
107. Vijay, K. Toll-Like Receptors in Immunity and Inflammatory Diseases: Past, Present, and Future. *Int. Immunopharmacol.* **2018**, *59*, 391–412.
108. Cario, E. Barrier-Protective Function of Intestinal Epithelial Toll-Like Receptor 2. *Mucosal Immunol.* **2008**, *1*, S62–S66.
109. Sepehri, Z.; Kiani, Z.; Nasiri, A.A.; et al. Toll-Like Receptor 2 and Type 2 Diabetes. *Cell Mol. Biol. Lett.* **2016**, *21*, 1–9.
110. Han, B.; Zhang, C.; Wang, X.; et al. The Functional Mechanisms of Toll-Like Receptor 3 and Its Implications in Digestive System Tumors. *Front. Biosci.* **2023**, *11*, 297.
111. Alexopoulou, L.; Holt, A.C.; Medzhitov, R.; et al. Recognition of Double-Stranded RNA and Activation of NF-κB by Toll-Like Receptor 3. *Nature* **2001**, *413*, 732–738.
112. Vaure, C.; Liu, Y. A Comparative Review of Toll-Like Receptor 4 Expression and Functionality in Different Animal Species. *Front. Immunol.* **2014**, *5*, 96623.
113. Miao, E.A.; Andersen-Nissen, E.; Warren, S.E.; et al. TLR5 and Ipaf: Dual Sensors of Bacterial Flagellin in the Innate Immune System. *Semin. Immunopathol.* **2007**, *29*, 275–283.
114. Lim, J.S.; Nguyen, K.C.T.; Han, J.M.; et al. Direct Regulation of TLR5 Expression by Caveolin-1. *Mol. Cells* **2015**, *38*, 1111–1117.
115. Noreen, M.; Arshad, M. Association of TLR1, TLR2, TLR4, TLR6, and TIRAP Polymorphisms with Disease Susceptibility. *Immunol. Res.* **2015**, *62*, 234–252.
116. Yeh, D.W.; Huang, L.R.; Chen, Y.W.; et al. Interplay between Inflammation and Stemness in Cancer Cells: The Role of Toll-Like Receptor Signaling. *J. Immunol. Res.* **2016**, *2016*, 368101.
117. Kang, J.Y.; Nan, X.; Jin, M.S.; et al. Recognition of Lipopeptide Patterns by Toll-Like Receptor 2–Toll-Like Receptor 6 Heterodimer. *Immunity* **2009**, *31*, 873–884.
118. Jackson, S.W.; Rovin, B.H. Resolving a Paradox between Mouse and Man: A Genetic Link between TLR7 and the Pathogenesis of Human Lupus Nephritis. *Kidney Int.* **2023**, *103*, 824–826.
119. Brown, G.J.; Cañete, P.F.; Wang, H.; et al. TLR7 Gain-of-Function Genetic Variation Causes Human Lupus. *Nature* **2022**, *605*, 349–356.

120. Heil, F.; Hemmi, H.; Hochrein, H.; et al. Species-Specific Recognition of Single-Stranded RNA via Toll-Like Receptor 7 and 8. *Science* **2004**, *303*, 1526–1529.
121. Huang, X.; Zhang, X.; Lu, M. Recent Trends in the Development of Toll-Like Receptor 7/8-Targeting Therapeutics. *Expert Opin. Drug Discov.* **2021**, *16*, 869–880.
122. Leite, F.R.; Enevold, C.; Bendtzen, K.; et al. Pattern Recognition Receptor Polymorphisms in Early Periodontitis. *J. Periodontol.* **2019**, *90*, 647–654.
123. Lund, J.; Sato, A.; Akira, S.; et al. Toll-Like Receptor 9–Mediated Recognition of Herpes Simplex Virus-2 by Plasmacytoid Dendritic Cells. *J. Exp. Med.* **2003**, *198*, 513–520.
124. Hess, N.J.; Jiang, S.; Li, X.; et al. TLR10 Is a B Cell Intrinsic Suppressor of Adaptive Immune Responses. *J. Immunol.* **2017**, *198*, 699–707.
125. Shukla, S.; Richardson, E.T.; Drage, M.G.; et al. Mycobacterium tuberculosis Lipoprotein and Lipoglycan Binding to Toll-Like Receptor 2 Correlates with Agonist Activity and Functional Outcomes. *Infect. Immun.* **2018**, *86*, e00312-18.
126. Sahasrabudhe, N.M.; Beukema, M.; Tian, L.; et al. Dietary Fiber Pectin Directly Blocks Toll-Like Receptor 2–1 and Prevents Doxorubicin-Induced Ileitis. *Front. Immunol.* **2018**, *9*, 383.
127. Raieli, S.; Trichot, C.; Korniotis, S.; et al. TLR1/2 Orchestrate Human Plasmacytoid Predendritic Cell Response to Gram+ Bacteria. *PLoS Biol.* **2019**, *17*, e3000209.
128. Zhu, J.; Li, G.; Gowda, K. Proinflammatory Responses by Glycosylphosphatidylinositols (GPIs) of Plasmodium falciparum Are Mainly Mediated through the Recognition of TLR2/TLR1. *Exp. Parasitol.* **2011**, *128*, 205–211.
129. Plantinga, T.S.; Johnson, M.D.; Scott, W.K.; et al. Toll-Like Receptor 1 Polymorphisms Increase Susceptibility to Candidemia. *J. Infect. Dis.* **2012**, *205*, 934–943.
130. Monlish, D.; Greenberg, Z.J.; Bhatt, S.; et al. TLR2/6 Signaling Promotes the Expansion of Premalignant Hematopoietic Stem and Progenitor Cells in the NUP98-HOXD13 Mouse Model of MDS. *Exp. Hematol.* **2020**, *88*, 42–55.
131. Su, L.; Wang, Y.; Wang, J.; et al. Structural Basis of TLR2/TLR1 Activation by the Synthetic Agonist Diprovocim. *J. Med. Chem.* **2019**, *62*, 2938–2949.
132. Takeuchi, O.; Kawai, T.; Mühlradt, P.F.; et al. Discrimination of Bacterial Lipoproteins by Toll-Like Receptor 6. *Int. Immunol.* **2001**, *13*, 933–940.
133. Yang, M.; Zheng, M.H.; Meng, X.T.; et al. Role of Toll-Like Receptors in the Pathogenesis of COVID-19: Current and Future Perspectives. *Scand. J. Immunol.* **2023**, *98*, e13282.
134. Frank, M.; Hennenberg, E.M.; Eyking, A.; et al. TLR Signaling Modulates Side Effects of Anticancer Therapy in the Small Intestine. *J. Immunol.* **2015**, *194*, 1983–1995.
135. Weinkove, R.; George, P.J.; Fyfe, R.; et al. A Phase 1 Dose Escalation Trial of Third-Generation CD19-Directed CAR T Cells Incorporating CD28 and Toll-Like Receptor 2 (TLR2) Intracellular Domains for Relapsed or Refractory B-Cell Non-Hodgkin Lymphomas (ENABLE). *Blood* **2023**, *142*, 890.
136. Kwok, Y.H.; Hutchinson, M.R.; Gentgall, M.; et al. Increased Responsiveness of Peripheral Blood Mononuclear Cells to in Vitro TLR 2, 4 and 7 Ligand Stimulation in Chronic Pain Patients. *PLoS One* **2012**, *7*, e44232.
137. Soberman, R.J.; Mackay, C.R.; Vaine, C.A.; et al. CD200R1 Supports HSV-1 Viral Replication and Licenses Pro-Inflammatory Signaling Functions of TLR2. *PLoS One* **2012**, *7*, e47740.
138. Tsai, S.Y.; Segovia, J.A.; Chang, T.H.; et al. Regulation of TLR3 Activation by S100A9. *J. Immunol.* **2015**, *195*, 4426–4437.
139. Lim, H.K.; Seppänen, M.; Hautala, T.; et al. TLR3 Deficiency in Herpes Simplex Encephalitis: High Allelic Heterogeneity and Recurrence Risk. *Neurology* **2014**, *83*, 1888–1897.
140. Chen, Y.; Lin, J.; Zhao, Y.; et al. Toll-Like Receptor 3 (TLR3) Regulation Mechanisms and Roles in Antiviral Innate Immune Responses. *J. Zhejiang Univ. Sci. B* **2021**, *22*, 609–632.
141. Park, B.S.; Lee, J.O. Recognition of Lipopolysaccharide Pattern by TLR4 Complexes. *Exp. Mol. Med.* **2013**, *45*, e66.
142. Opal, S.M.; Laterre, P.F.; Francois, B.; et al. Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients with Severe Sepsis: The ACCESS Randomized Trial. *JAMA* **2013**, *309*, 1154–1162.
143. den Dekker, W.K.; Cheng, C.; Pasterkamp, G.; et al. Toll Like Receptor 4 in Atherosclerosis and Plaque Destabilization. *Atherosclerosis* **2010**, *209*, 314–320.
144. Oliveira, A.A.d.; Faustino, J.; Lima, M.E.d.; et al. Unveiling the Interplay Between the TLR4/MD2 Complex and HSP70 in the Human Cardiovascular System: A Computational Approach. *Int. J. Mol. Sci.* **2019**, *20*, 3121.
145. O'Neill, S.; Humphries, D.C.; Tse, G.; et al. Heat Shock Protein 90 Inhibition Abrogates TLR4-Mediated NF-κB

Activity and Reduces Renal Ischemia-Reperfusion Injury. *Sci. Rep.* **2015**, *5*, 12958.
146. Xu, Z.; Xie, M.M.; Xie, C.L.; et al. Deep-Sea-Derived Isobisvertinol Targets TLR4 to Exhibit Neuroprotective Activity via Anti-Inflammatory and Ferroptosis-Inhibitory Effects. *Mar. Drugs* **2025**, *23*, 49.
147. Zuo, W.; Zhao, J.; Zhang, J.; et al. MD2 Contributes to the Pathogenesis of Perioperative Neurocognitive Disorder via the Regulation of α5GABAA Receptors in Aged Mice. *J. Neuroinflammation* **2021**, *18*, 1.
148. Stewart, C.R.; Stuart, L.M.; Wilkinson, K.; et al. CD36 Ligands Promote Sterile Inflammation Through Assembly of a Toll-Like Receptor 4 and 6 Heterodimer. *Nat. Immunol.* **2010**, *11*, 155–161.
149. Shmuel-Galia, L.; Klug, Y.; Porat, Z.; et al. Intramembrane Attenuation of the TLR4-TLR6 Dimer Impairs Receptor Assembly and Reduces Microglia-Mediated Neurodegeneration. *J. Biol. Chem.* **2017**, *292*, 13415–13427.
150. Zhou, L.; Wang, X.; Xiao, Q.; et al. Flagellin Restricts HIV-1 Infection of Macrophages Through Modulation of Viral Entry Receptors and CC Chemokines. *Viruses* **2024**, *16*, 1063.
151. Zhao, Y.; Li, Z.; Zhu, X.; et al. Improving Immunogenicity and Safety of Flagellin as Vaccine Carrier by High-Density Display on Virus-Like Particle Surface. *Biomaterials* **2020**, *249*, 120030.
152. Treanor, J.J.; Taylor, D.N.; Tussey, L.; et al. Safety and Immunogenicity of a Recombinant Hemagglutinin Influenza-Flagellin Fusion Vaccine (VAX125) in Healthy Young Adults. *Vaccine* **2010**, *28*, 8268–8274.
153. Gewirtz, A.T.; Navas, T.A.; Lyons, S.; et al. Cutting Edge: Bacterial Flagellin Activates Basolaterally Expressed TLR5 to Induce Epithelial Proinflammatory Gene Expression. *J. Immunol.* **2001**, *167*, 1882–1885.
154. Afzal, H.; Murtaza, A.; Cheng, L.T. Structural Engineering of Flagellin as Vaccine Adjuvant: Quest for the Minimal Domain of Flagellin for TLR5 Activation. *Mol. Biol. Rep.* **2025**, *52*, 104.
155. Takeuchi, O.; Sato, S.; Horiuchi, T.; et al. Cutting Edge: Role of Toll-Like Receptor 1 in Mediating Immune Response to Microbial Lipoproteins. *J. Immunol.* **2002**, *169*, 10–14.
156. Love, W.; Dobbs, N.; Tabor, L.; et al. Toll-Like Receptor 2 (TLR2) Plays a Major Role in Innate Resistance in the Lung Against Murine Mycoplasma. *PLoS One* **2010**, *5*, e10739.
157. Diebold, S.S.; Kaisho, T.; Hemmi, H.; et al. Innate Antiviral Responses by Means of TLR7-Mediated Recognition of Single-Stranded RNA. *Science* **2004**, *303*, 1529–1531.
158. Adams, S.; Dewan, Z.; Meng, T.; et al. Evaluation of Toll-Like Receptor (TLR)-7 Agonist Imiquimod Applied Topically to Breast Cancer Chest Wall Recurrences or Skin Metastases. *J. Clin. Oncol.* **2010**, *28*, TPS138.
159. Frega, G.; Wu, Q.; Le Naour, J.; et al. Trial Watch: Experimental TLR7/TLR8 Agonists for Oncological Indications. *Oncoimmunology* **2020**, *9*, 1796002.
160. Paul, A.M.; Acharya, D.; Le, L.; et al. TLR8 Couples SOCS-1 and Restrains TLR7-Mediated Antiviral Immunity Exacerbating West Nile Virus Infection in Mice. *J. Immunol.* **2016**, *197*, 4425–4435.
161. Bender, A.T.; Tzvetkov, E.; Pereira, A.; et al. TLR7 and TLR8 Differentially Activate the IRF and NF-κB Pathways in Specific Cell Types to Promote Inflammation. *ImmunoHorizons* **2020**, *4*, 93–107.
162. Finberg, R.W.; Wang, J.P.; Kurt-Jones, E.A. Toll-Like Receptors and Viruses. *Rev. Med. Virol.* **2007**, *17*, 35–43.
163. Kawai, T.; Akira, S. TLR Signaling. *Cell Death Differ.* **2006**, *13*, 816–825.
164. Wang, Y.; Yang, H.; Li, H.; et al. Development of a Novel TLR8 Agonist for Cancer Immunotherapy. *Mol. Biomed.* **2020**, *1*, 6.
165. Urban-Wojciuk, Z.; Khan, M.M.; Oyler, B.L.; et al. The Role of TLRs in Anti-Cancer Immunity and Tumor Rejection. *Front. Immunol.* **2019**, *10*, 2388.
166. McGowan, D.C. Latest Advances in Small Molecule TLR7/8 Agonist Drug Research. *Curr. Top. Med. Chem.* **2019**, *19*, 2228–2238.
167. Jin, Y.; Zhuang, Y.; Dong, X.; et al. Development of CpG Oligodeoxynucleotide TLR9 Agonists in Anti-Cancer Therapy. *Expert Rev. Anticancer Ther.* **2021**, *21*, 841–851.
168. Kumagai, Y.; Takeuchi, O.; Akira, S. TLR9 as a Key Receptor for the Recognition of DNA. *Adv. Drug Deliv. Rev.* **2008**, *60*, 795–804.
169. Babenko, V.N.; Chadaeva, I.V.; Orlov, Y.L. Genomic Landscape of CpG Rich Elements in Human. *BMC Evol. Biol.* **2017**, *17*, 19.
170. Jeon, D.; Hill, E.; McNeel, D.G. Toll-Like Receptor Agonists as Cancer Vaccine Adjuvants. *Hum. Vaccin. Immunother.* **2024**, *20*, 2297453.
171. Wagner, H. The Sweetness of the DNA Backbone Drives Toll-Like Receptor 9. *Curr. Opin. Immunol.* **2008**, *20*, 396–400.
172. Guan, Y.; Ranoa, D.R.; Jiang, S.; et al. Human TLRs 10 and 1 Share Common Mechanisms of Innate Immune Sensing but Not Signaling. *J. Immunol.* **2010**, *184*, 5094–5103.
173. Su, S.B.; Tao, L.; Deng, Z.P.; et al. TLR10: Insights, Controversies and Potential Utility as a Therapeutic Target.

Scand. J. Immunol. **2021**, *93*, e12988.
174. Oosting, M.; Cheng, S.C.; Bolscher, J.M.; et al. Human TLR10 Is an Anti-Inflammatory Pattern-Recognition Receptor. *Proc. Natl. Acad. Sci.* **2014**, *111*, E4478–E4484.
175. Hasan, U.; Chaffois, C.; Gaillard, C.; et al. Human TLR10 Is a Functional Receptor, Expressed by B Cells and Plasmacytoid Dendritic Cells, Which Activates Gene Transcription Through MyD88. *J. Immunol.* **2005**, *174*, 2942–2950.
176. Fore, F.; Indriputri, C.; Mamutse, J.; et al. TLR10 and Its Unique Anti-Inflammatory Properties and Potential Use as a Target in Therapeutics. *Immune Netw.* **2020**, *20*, e21.
177. Hess, N.J.; Felicelli, C.; Grage, J.; et al. TLR10 Suppresses the Activation and Differentiation of Monocytes with Effects on DC-Mediated Adaptive Immune Responses. *J. Leukoc. Biol.* **2017**, *101*, 1245–1252.
178. Deb, P.; Singh, S.; Kalyoussef, E.; et al. TLR10 (CD290) Is a Regulator of Immune Responses in Human Plasmacytoid Dendritic Cells. *J. Immunol.* **2024**, *213*, 577–587.
179. Sindhu, S.; Akhter, N.; Kochumon, S.; et al. Increased Expression of the Innate Immune Receptor TLR10 in Obesity and Type-2 Diabetes: Association with ROS-Mediated Oxidative Stress. *Cell Physiol. Biochem.* **2018**, *45*, 572–590.
180. Bui, F.Q.; Almeida-da-Silva, C.L.C.; Huynh, B.; et al. Association Between Periodontal Pathogens and Systemic Disease. *Biomed. J.* **2019**, *42*, 27–35.
181. Sahingur, S.E.; Yeudall, W.A. Chemokine Function in Periodontal Disease and Oral Cavity Cancer. *Front. Immunol.* **2015**, *6*, 140295.
182. Williams, J.M.; Greenslade, J.H.; McKenzie, J.V.; et al. Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction: Insights from a Prospective Database of ED Patients with Infection. *Chest* **2017**, *151*, 586–596.
183. Isola, G.; Santonocito, S.; Lupi, S.M.; et al. Periodontal Health and Disease in the Context of Systemic Diseases. *Mediators Inflamm.* **2023**, *2023*, 1–15.
184. De Nardo, D. Toll-Like Receptors: Activation, Signalling and Transcriptional Modulation. *Cytokine* **2015**, *74*, 181–189.
185. Fernandes, D.; Khambata, R.S.; Massimo, G.; et al. Local Delivery of Nitric Oxide Prevents Endothelial Dysfunction in Periodontitis. *Pharmacol. Res.* **2023**, *188*, 106616.
186. Zou, J.; Zeng, Z.; Xie, W.; et al. Immunotherapy with Regulatory T and B Cells in Periodontitis. *Int. Immunopharmacol.* **2022**, *109*, 108797.
187. Li, Y.; Chen, Y.; Cai, G.; et al. Roles of Trained Immunity in the Pathogenesis of Periodontitis. *J. Periodontal Res.* **2023**, *58*, 864–873.
188. Disale, P.R.; Zope, S.; Suragimath, G.; et al. Toll-Like Receptors: Molecular Microbe Sensors in Periodontium. *World J. Dent.* **2019**, *10*, 396–401.
189. Mahanonda, R.; Pichyangkul, S. Toll-Like Receptors and Their Role in Periodontal Health and Disease. *Periodontol. 2000* **2007**, *43*, 41–55.
190. Goulopoulou, S.; McCarthy, C.G.; Webb, R.C. Toll-Like Receptors in the Vascular System: Sensing the Dangers Within. *Pharmacol. Rev.* **2016**, *68*, 142–167.
191. Kim, H.J.; Kim, H.; Lee, J.H.; et al. Toll-Like Receptor 4 (TLR4): New Insight Immune and Aging. *Immun. Ageing* **2023**, *20*, 67.
192. O'Neill, L.A.; Bowie, A.G. The Family of Five: TIR-Domain-Containing Adaptors in Toll-Like Receptor Signalling. *Nat. Rev. Immunol.* **2007**, *7*, 353–364.
193. Ullah, M.O.; Sweet, M.J.; Mansell, A.; et al. TRIF-Dependent TLR Signaling, Its Functions in Host Defense and Inflammation, and Its Potential as a Therapeutic Target. *J. Leukoc. Biol.* **2016**, *100*, 27–45.
194. Zorn, B.; Virant-Klun, I.; Meden-Vrtovec, H. Semen Granulocyte Elastase: Its Relevance for the Diagnosis and Prognosis of Silent Genital Tract Inflammation. *Hum. Reprod.* **2000**, *15*, 1978–1984.
195. Wang, C.; Chen, T.; Zhang, J.; et al. The E3 Ubiquitin Ligase Nrdp1 Preferentially Promotes TLR-Mediated Production of Type I Interferon. *Nat. Immunol.* **2009**, *10*, 744–752.
196. De Nardo, D.; Balka, K.R.; Gloria, Y.C.; et al. Interleukin-1 Receptor–Associated Kinase 4 (IRAK4) Plays a Dual Role in Myddosome Formation and Toll-Like Receptor Signaling. *J. Biol. Chem.* **2018**, *293*, 15195–15207.
197. Zhang, G.; Ghosh, S. Negative Regulation of Toll-Like Receptor-Mediated Signaling by Tollip. *J. Biol. Chem.* **2002**, *277*, 7059–7065.
198. Zhang, J.; Zao, X.; Zhang, J.; et al. Is It Possible to Intervene Early Cirrhosis by Targeting Toll-Like Receptors to Rebalance the Intestinal Microbiome? *Int. Immunopharmacol.* **2023**, *115*, 109627.
199. Lin, M.; Ji, X.; Lv, Y.; et al. The Roles of TRAF3 in Immune Responses. *Dis. Markers* **2023**, *2023*, 787803.

200. Xia, P.; Wu, Y.; Lian, S.; et al. Research Progress on Toll-Like Receptor Signal Transduction and Its Roles in Antimicrobial Immune Responses. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 5341–5355.
201. Farooq, M.; Batool, M.; Kim, M.S.; et al. Toll-Like Receptors as a Therapeutic Target in the Era of Immunotherapies. *Front. Cell Dev. Biol.* **2021**, *9*, 756315.
202. Roshan, M.H.; Tambo, A.; Pace, N.P. The Role of TLR2, TLR4, and TLR9 in the Pathogenesis of Atherosclerosis. *Int. J. Inflamm.* **2016**, *2016*, 532832.
203. Rogero, M.M.; Calder, P.C. Obesity, Inflammation, Toll-Like Receptor 4 and Fatty Acids. *Nutrients* **2018**, *10*, 432.
204. Chen, E.; Chen, C.; Niu, Z.; et al. Poly (I:C) Preconditioning Protects the Heart against Myocardial Ischemia/Reperfusion Injury through TLR3/PI3K/Akt-Dependent Pathway. *Signal Transduct. Target. Ther.* **2020**, *5*, 216.
205. Lei, Y.Q.; Wan, Y.T.; Liang, G.T.; et al. Extracellular RNAs/TLR3 Signaling Contributes to Acute Intestinal Injury Induced by Intestinal Ischemia Reperfusion in Mice. *Biochim. Biophys. Acta Mol. Basis Dis.* **2023**, *1869*, 166790.
206. Sidletskaya, K.; Vitkina, T.; Denisenko, Y. The Role of Toll-Like Receptors 2 and 4 in the Pathogenesis of Chronic Obstructive Pulmonary Disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2020**, *15*, 1481–1493.
207. Esposito, S.; Tenconi, R.; Lelii, M.; et al. Possible Molecular Mechanisms Linking Air Pollution and Asthma in Children. *BMC Pulm. Med.* **2014**, *14*, 1–8.
208. Frosali, S.; Pagliari, D.; Gambassi, G.; et al. How the Intricate Interaction among Toll-Like Receptors, Microbiota, and Intestinal Immunity Can Influence Gastrointestinal Pathology. *J. Immunol. Res.* **2015**, *2015*, 89821.
209. Fang, Y.; Yan, C.; Zhao, Q.; et al. The Association between Gut Microbiota, Toll-Like Receptors, and Colorectal Cancer. *Clin. Med. Insights Oncol.* **2022**, *16*, 11795549221130549.
210. Adhikarla, S.V.; Jha, N.K.; Goswami, V.K.; et al. TLR-Mediated Signal Transduction and Neurodegenerative Disorders. *Brain Sci.* **2021**, *11*, 1373.
211. Tansey, M.G.; Wallings, R.L.; Houser, M.C.; et al. Inflammation and Immune Dysfunction in Parkinson Disease. *Nat. Rev. Immunol.* **2022**, *22*, 657–673.
212. Kwon, S.J.; Khan, M.S.; Kim, S.G. Intestinal Inflammation and Regeneration–Interdigitating Processes Controlled by Dietary Lipids in Inflammatory Bowel Disease. *Int. J. Mol. Sci.* **2024**, *25*, 1311.
213. Robertson, S.A.; Hutchinson, M.R.; Rice, K.C.; et al. Targeting Toll-Like Receptor-4 to Tackle Preterm Birth and Fetal Inflammatory Injury. *Clin. Transl. Immunol.* **2020**, *9*, e1121.
214. Wang, S.; Zhang, K.; Yao, Y.; et al. Bacterial Infections Affect Male Fertility: A Focus on the Oxidative Stress-Autophagy Axis. *Front. Cell Dev. Biol.* **2021**, *9*, 727812.
215. Dutta, S.; Sengupta, P.; Slama, P.; et al. Oxidative Stress, Testicular Inflammatory Pathways, and Male Reproduction. *Int. J. Mol. Sci.* **2021**, *22*, 10043.
216. Zhu, W.; Meng, L.; Jiang, C.; et al. Arthritis Is Associated with T-Cell-Induced Upregulation of Toll-Like Receptor 3 on Synovial Fibroblasts. *Arthritis Res. Ther.* **2011**, *13*, R103.
217. Alzabin, S.; Kong, P.; Medghalchi, M.; et al. Investigation of the Role of Endosomal Toll-Like Receptors in Murine Collagen-Induced Arthritis Reveals a Potential Role for TLR7 in Disease Maintenance. *Arthritis Res. Ther.* **2012**, *14*, R142.
218. Meng, L.; Zhu, W.; Jiang, C.; et al. Toll-Like Receptor 3 Upregulation in Macrophages Participates in the Initiation and Maintenance of Pristane-Induced Arthritis in Rats. *Arthritis Res. Ther.* **2010**, *12*, R103.
219. Soraci, L.; Gambuzza, M.E.; Biscetti, L.; et al. Toll-Like Receptors and NLRP3 Inflammasome-Dependent Pathways in Parkinson's Disease: Mechanisms and Therapeutic Implications. *J. Neurol.* **2022**, *270*, 1346–1360.
220. Dabi, Y.T.; Ajagbe, A.O.; Degechisa, S.T. Toll-Like Receptors in Pathogenesis of Neurodegenerative Diseases and Their Therapeutic Potential. *Immun. Inflamm. Dis.* **2023**, *11*, 1430.
221. Mekhemar, M.; Terheyden, I.; Dörfer, C.E.; et al. Inflammatory Modulation of Toll-Like Receptors in Periodontal Ligament Stem Cells: Implications for Periodontal Therapy. *Cells* **2025**, *14*, 432.
222. Nickerson, K.M.; Christensen, S.R.; Shupe, J.; et al. TLR9 Regulates TLR7- and MyD88-Dependent Autoantibody Production and Disease in a Murine Model of Lupus. *J. Immunol.* **2010**, *184*, 1840–1848.
223. Yogarajah, M.; Sivasambu, B.; Jaffe, E. Bullous Systemic Lupus Erythematosus Associated with Esophagitis Dissecans Superficialis. *Case Rep. Rheumatol.* **2015**, *2015*, 930683.
224. Hajishengallis, G.; Lambris, J.D. Microbial Manipulation of Receptor Crosstalk in Innate Immunity. *Nat. Rev. Immunol.* **2011**, *11*, 187–200.
225. Walter, S.; Letiembre, M.; Liu, Y.; et al. Role of the Toll-Like Receptor 4 in Neuroinflammation in Alzheimer's

Disease. *Cell. Physiol. Biochem.* **2007**, *20*, 947–956.
226. Scholtzova, H.; Chianchiano, P.; Pan, J.; et al. Amyloid β and Tau Alzheimer's Disease Related Pathology Is Reduced by Toll-Like Receptor 9 Stimulation. *Acta Neuropathol. Commun.* **2014**, *2*, 101.
227. Calvo-Rodríguez, M.; Fuente, C.L.; García-Durillo, M.; et al. Aging and Amyloid β Oligomers Enhance TLR4 Expression, LPS-Induced Ca2+ Responses, and Neuron Cell Death in Cultured Rat Hippocampal Neurons. *J. Neuroinflammation* **2017**, *14*, 24.
228. Wang, M.M.; Miao, D.; Cao, X.P.; et al. Innate Immune Activation in Alzheimer's Disease. *Ann. Transl. Med.* **2018**, *6*, 177.
229. Kay, E.; Scotland, R.S.; Whiteford, J.R. Toll-Like Receptors: Role in Inflammation and Therapeutic Potential. *Biofactors* **2014**, *40*, 284–294.
230. Heinz, L.X.; Lee, J.; Kapoor, U.; et al. TASL Is the SLC15A4-Associated Adaptor for IRF5 Activation by TLR7–9. *Nature* **2020**, *581*, 316–322.
231. Odhams, C.A.; Roberts, A.L.; Vester, S.K.; et al. Interferon Inducible X-Linked Gene CXorf21 May Contribute to Sexual Dimorphism in Systemic Lupus Erythematosus. *Nat. Commun.* **2019**, *10*, 2164.
232. Caielli, S.; Wan, Z.; Pascual, V. Systemic Lupus Erythematosus Pathogenesis: Interferon and Beyond. *Nat. Rev. Immunol.* **2023**, *41*, 533–560.
233. Ban, T.; Sato, G.; Nishiyama, A.; et al. Lyn Kinase Suppresses the Transcriptional Activity of IRF5 in the TLR-MyD88 Pathway to Restrain the Development of Autoimmunity. *Immunity* **2016**, *45*, 319–332.
234. McGarry, T.; Biniecka, M.; Gao, W.; et al. Resolution of TLR2-Induced Inflammation through Manipulation of Metabolic Pathways in Rheumatoid Arthritis. *Sci. Rep.* **2017**, *7*, 43165.
235. Kalliolias, G.D.; Basdra, E.K.; Papavassiliou, A.G. Targeting TLR Signaling Cascades in Systemic Lupus Erythematosus and Rheumatoid Arthritis: An Update. *Biomedicines* **2024**, *12*, 138.
236. Chávez-Sánchez, L.; Madrid-Miller, A.; Chávez-Rueda, K.; et al. Activation of TLR2 and TLR4 by Minimally Modified Low-Density Lipoprotein in Human Macrophages and Monocytes Triggers the Inflammatory Response. *Hum. Immunol.* **2010**, *71*, 737–744.
237. Schoneveld, A.H.; Hoefer, I.; Sluijter, J.P.; et al. Atherosclerotic Lesion Development and Toll-Like Receptor 2 and 4 Responsiveness. *Atherosclerosis* **2008**, *197*, 95–104.
238. Shafeghat, M.; Kazemian, S.; Aminorroaya, A.; et al. Toll-Like Receptor 7 Regulates Cardiovascular Diseases. *Int. Immunopharmacol.* **2022**, *113*, 109390.
239. Cole, J.E.; Navin, T.J.; Cross, A.J.; et al. Unexpected Protective Role for Toll-Like Receptor 3 in the Arterial Wall. *Proc. Natl. Acad. Sci.* **2011**, *108*, 2372–2377.
240. Koulis, C.; Chen, Y.C.; Hausding, C.; et al. Protective Role for Toll-Like Receptor 9 in the Development of Atherosclerosis in Apolipoprotein E-Deficient Mice. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 516–525.
241. Rajendran, M.; Sivasankar, K.; Subbarayan, S. Toll Gates: An Emerging Therapeutic Target. *J. Indian Soc. Periodontol.* **2014**, *18*, 686.
242. Liao, W.L.; Chen, R.H.; Lin, H.J.; et al. Toll-Like Receptor Gene Polymorphisms Are Associated with Susceptibility to Graves' Ophthalmopathy in Taiwan Males. *BMC Med. Genet.* **2010**, *11*, 154.
243. Yılmaz, B.; Emingil, G.; Öztürk, V.Ö.; et al. Gingival Crevicular Fluid Levels of TLR-9, AIM-2, and ZBP-1 in Periodontal Diseases. *Oral Dis.* **2024**, *31*, 941–948.
244. Zeng, W.; Liu, G.; Luan, Q.; et al. Epstein-Barr Virus Promotes Inflammatory Cytokine Production in Human Gingival Fibroblasts. *Int. Dent. J.* **2024**, *74*, 607–615.
245. Rose, W.A., II; Sakamoto, K.; Leifer, C.A. TLR9 Is Important for Protection Against Intestinal Damage and for Intestinal Repair. *Sci. Rep.* **2012**, *2*, 574.
246. Coppo, R.; Camilla, R.; Amore, A.; et al. Toll-Like Receptor 4 Expression Is Increased in Circulating Mononuclear Cells of Patients with Immunoglobulin A Nephropathy. *Clin. Exp. Immunol.* **2009**, *159*, 73–81.
247. Ciferská, H.; Honsová, E.; Lodererová, A.; et al. Does the Renal Expression of Toll-Like Receptors Play a Role in Patients with IgA Nephropathy? *J. Nephrol.* **2019**, *33*, 307–316.
248. Nakata, J.; Suzuki, Y.; Suzuki, H.; et al. Changes in Nephritogenic Serum Galactose-Deficient IgA1 in IgA Nephropathy Following Tonsillectomy and Steroid Therapy. *PLoS One* **2014**, *9*, e89707.
249. Zheng, N.; Xie, K.; Ye, H.; et al. TLR7 in B Cells Promotes Renal Inflammation and Gd-IgA1 Synthesis in IgA Nephropathy. *JCI Insight* **2020**, *5*, e139081.
250. Zou, M.; Guo, K.; Qian, D.; et al. Network Pharmacological Analysis of Hydroxychloroquine Intervention in the Treatment of IgA Nephropathy. *Curr. Pharm. Des.* **2023**, *31*, 730–740.
251. El-Sayed, K.M.F.; Mekhemar, M.; Adam-Klages, S.; et al. TLR Expression Profile of Human Gingival Margin-Derived Stem Progenitor Cells. *Med. Oral Patol. Oral Cir. Bucal* **2016**, *21*, e30–e38.

252. Cario, E. Toll-Like Receptors in Inflammatory Bowel Diseases: A Decade Later. *Inflamm. Bowel Dis.* **2010**, *16*, 1583–1597.
253. Ren, J.; Chen, X.; Chen, Z.J. IKKβ Is an IRF5 Kinase That Instigates Inflammation. *Proc. Natl. Acad. Sci.* **2014**, *111*, 17438–17443.
254. Feng, S.; Zhang, C.; Chen, S.; et al. TLR5 Signaling in the Regulation of Intestinal Mucosal Immunity. *J. Inflamm. Res.* **2023**, *16*, 2491–2501.
255. Guo, J.; Liao, M.; Wang, J. TLR4 Signaling in the Development of Colitis-Associated Cancer and Its Possible Interplay with MicroRNA-155. *Cell Commun. Signal.* **2021**, *19*, 90.
256. Schmitt, H.; Ulmschneider, J.; Billmeier, U.; et al. The TLR9 Agonist Cobitolimod Induces IL10-Producing Wound Healing Macrophages and Regulatory T Cells in Ulcerative Colitis. *J. Crohns Colitis* **2019**, *14*, 508–524.
257. Chung, L.Y.R.; Lin, Y.T.; Liu, C.; et al. Neuroinflammation Upregulated Neuronal Toll-Like Receptors 2 and 4 to Drive Synucleinopathy in Neurodegeneration. *Front. Pharmacol.* **2022**, *13*, 845930.
258. Maatouk, L.; Compagnion, A.C.; Sauvage, M.C.; et al. TLR9 Activation via Microglial Glucocorticoid Receptors Contributes to Degeneration of Midbrain Dopamine Neurons. *Nat. Commun.* **2018**, *9*, 2450.
259. Leventhal, J.S.; Schröppel, B. Toll-Like Receptors in Transplantation: Sensing and Reacting to Injury. *Kidney Int.* **2012**, *81*, 826–832.
260. Brentano, F.; Kyburz, D.; Gay, S. Toll-Like Receptors and Rheumatoid Arthritis. *Methods Mol. Biol.* **2009**, *517*, 329–343.
261. Abdollahi-Roodsaz, S.; Joosten, L.A.; Koenders, M.I.; et al. Stimulation of TLR2 and TLR4 Differentially Skews the Balance of T Cells in a Mouse Model of Arthritis. *J. Clin. Invest.* **2008**, *118*, 205–216.
262. Kužnik, A.; Benčina, M.; Švajger, U.; et al. Mechanism of Endosomal TLR Inhibition by Antimalarial Drugs and Imidazoquinolines. *J. Immunol.* **2011**, *186*, 4794–4804.
263. Chen, F.; Zou, L.; Williams, B.; et al. Targeting Toll-Like Receptors in Sepsis: From Bench to Clinical Trials. *Antioxid. Redox Signal.* **2021**, *35*, 1324–1339.
264. Tilstra, J.S.; Kim, M.J.; Gordon, R.A.; et al. B Cell-Intrinsic Myd88 Regulates Disease Progression in Murine Lupus. *J. Exp. Med.* **2023**, *220*, e20231427.
265. Zhang, Y.; Liu, J.; Wang, C.; et al. Toll-Like Receptors Gene Polymorphisms in Autoimmune Disease. *Front. Immunol.* **2021**, *12*, 738532.
266. Smith, N.; Rodero, M.P.; Bekaddour, N.; et al. Control of TLR7-Mediated Type I IFN Signaling in pDCs Through CXCR4 Engagement—A New Target for Lupus Treatment. *Sci. Adv.* **2019**, *5*, eaav9019.
267. Zhu, J.; Mohan, C. Toll-Like Receptor Signaling Pathways—Therapeutic Opportunities. *Mediators Inflamm.* **2010**, *2010*, 781235.
268. Gao, W.; Xiong, Y.; Li, Q.; et al. Inhibition of Toll-Like Receptor Signaling as a Promising Therapy for Inflammatory Diseases: A Journey from Molecular to Nano Therapeutics. *Front. Physiol.* **2017**, *8*, 508.
269. Santiago-Raber, M.L.; Dunand-Sauthier, I.; Wu, T.; et al. Critical Role of TLR7 in the Acceleration of Systemic Lupus Erythematosus in TLR9-Deficient Mice. *J. Autoimmun.* **2010**, *34*, 339–348.
270. Wang, X.; Smith, C.; Yin, H. Targeting Toll-Like Receptors with Small Molecule Agents. *Chem. Soc. Rev.* **2013**, *42*, 4859–4872.
271. Lee, Y.H.; Song, G.G. Systemic Lupus Erythematosus and Toll-Like Receptor 9 Polymorphisms: A Meta-Analysis of Genetic Association Studies. *Lupus* **2023**, *32*, 964–973.
272. Yun, T.J.; Igarashi, S.; Zhao, H.; et al. Human Plasmacytoid Dendritic Cells Mount a Distinct Antiviral Response to Virus-Infected Cells. *Sci. Immunol.* **2021**, *6*, eabc1234.
273. Krug, A.; French, A.R.; Barchet, W.; et al. TLR9-Dependent Recognition of MCMV by IPC and DC Generates Coordinated Cytokine Responses That Activate Antiviral NK Cell Function. *Immunity* **2004**, *21*, 107–119.
274. Ma, Y.; He, B. Recognition of Herpes Simplex Viruses: Toll-Like Receptors and Beyond. *J. Mol. Biol.* **2014**, *426*, 1133–1147.
275. Rallabhandi, P.; Phillips, R.L.; Boukhvalova, M.S.; et al. Respiratory Syncytial Virus Fusion Protein-Induced Toll-Like Receptor 4 (TLR4) Signaling Is Inhibited by the TLR4 Antagonists Rhodobacter sphaeroides Lipopolysaccharide and Eritoran (E5564) and Requires Direct Interaction with MD-2. *mBio* **2012**, *3*, e00218-12.
276. Saidoune, F.; Lee, D.; Di Domizio, J.; et al. Enhanced TLR7-Dependent Production of Type I Interferon by pDCs Underlies Pandemic Chilblains. *J. Exp. Med.* **2025**, *222*, e20231467.
277. Kader, M.; Smith, A.P.; Guiducci, C.; et al. Blocking TLR7- and TLR9-Mediated IFN-α Production by Plasmacytoid Dendritic Cells Does Not Diminish Immune Activation in Early SIV Infection. *PLoS Pathog.* **2013**, *9*,

e1003530.
278. Abston, E.D.; Coronado, M.J.; Bucek, A.; et al. TLR3 Deficiency Induces Chronic Inflammatory Cardiomyopathy in Resistant Mice Following Coxsackievirus B3 Infection: Role for IL-4. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2013**, *304*, R267–R277.
279. Zhao, Z.; Cai, T.Z.; Lu, Y.; et al. Coxsackievirus B3 Induces Viral Myocarditis by Upregulating Toll-Like Receptor 4 Expression. *Biochemistry* **2015**, *80*, 455–462.
280. Zheng, S.Y.; Dong, J.Z. Role of Toll-Like Receptors and Th Responses in Viral Myocarditis. *Front. Immunol.* **2022**, *13*, 843891.
281. Yajima, T.; Knowlton, K.U. Viral Myocarditis: From the Perspective of the Virus. *Circulation* **2009**, *119*, 2615–2624.
282. Li, S.; Yan, Y.; Xu, W.; et al. MicroRNA-146a Represses Mycobacteria-Induced Inflammatory Response and Facilitates Bacterial Replication via Targeting IRAK-1 and TRAF-6. *PLoS One* **2013**, *8*, e81438.
283. Meng, L.; Zhang, P.; Li, C.; et al. miRNA-133 Augments Coelomocyte Phagocytosis in Bacteria-Challenged Apostichopus japonicus via Targeting the TLR Component of IRAK-1 In Vitro and In Vivo. *Sci. Rep.* **2015**, *5*, 12608.
284. Luo, X.; Yang, W.; Ye, D.Q.; et al. A Functional Variant in microRNA-146a Promoter Modulates Its Expression and Confers Disease Risk for Systemic Lupus Erythematosus. *PLoS Genet.* **2011**, *7*, e1002128.
285. Stanczyk, J.; Pedrioli, D.M.; Brentano, F.; et al. Altered Expression of microRNA in Synovial Fibroblasts and Synovial Tissue in Rheumatoid Arthritis. *Arthritis Rheum.* **2008**, *58*, 1001–1009.
286. Taganov, K.D.; Boldin, M.P.; Chang, K.J.; et al. NF-κB-Dependent Induction of microRNA miR-146, an Inhibitor Targeted to Signaling Proteins of Innate Immune Responses. *Proc. Natl. Acad. Sci.* **2006**, *103*, 12481–12486.
287. Juknat, A.; Gao, F.; Coppola, G.; et al. miRNA Expression Profiles and Molecular Networks in Resting and LPS-Activated BV-2 Microglia—Effect of Cannabinoids. *PLoS One* **2019**, *14*, e0212039.
288. Selvaskandan, H.; Pawluczyk, I.; Barratt, J. MicroRNAs: A New Avenue to Understand, Investigate and Treat Immunoglobulin A Nephropathy? *Clin. Kidney J.* **2017**, *11*, 29–37.
289. Chassin, C.; Kocur, M.; Pott, J.; et al. miR-146a Mediates Protective Innate Immune Tolerance in the Neonate Intestine. *Cell Host Microbe* **2010**, *8*, 358–368.
290. Bayraktar, R.; Bertilaccio, M.T.S.; Calin, G.A. The Interaction Between Two Worlds: MicroRNAs and Toll-Like Receptors. *Front. Immunol.* **2019**, *10*, 1053.
291. Wallach, T.; Wetzel, M.; Dembny, P.; et al. Identification of CNS Injury-Related microRNAs as Novel Toll-Like Receptor 7/8 Signaling Activators by Small RNA Sequencing. *Cells* **2020**, *9*, 186.
292. Przybyciński, J.; Czerewaty, M.; Kwiatkowska, E.; et al. MicroRNAs miR-148a-3p, miR-425-3p, and miR-20a-5p in Patients with IgA Nephropathy. *Genes* **2025**, *16*, 125.
293. Yao, X.; Zhai, Y.; An, H.; et al. MicroRNAs in IgA Nephropathy. *Ren. Fail.* **2021**, *43*, 1298–1310.
294. Pawluczyk, I.; Nicholson, M.; Barbour, S.; et al. A Pilot Study to Predict Risk of IgA Nephropathy Progression Based on miR-204 Expression. *Kidney Int. Rep.* **2021**, *6*, 2179–2188.
295. El-Ekiaby, N.; Hamdi, N.; Negm, M.; et al. Repressed Induction of Interferon-Related microRNAs miR-146a and miR-155 in Peripheral Blood Mononuclear Cells Infected with HCV Genotype 4. *FEBS Open Bio* **2012**, *2*, 179–186.
296. Zhong, Y.; Zhang, C.; Zheng, X.; et al. Mechanism Research on MicroRNA-669f-5p/Deoxycytidylate Deaminase Axis Mediating Sevoflurane-Induced Cognitive Dysfunction in Aged Mice. *Fundam. Clin. Pharmacol.* **2024**, *38*, 1031–1044.
297. Yan, Y.; Lu, K.; Ye, T.; et al. MicroRNA-223 Attenuates LPS-Induced Inflammation in an Acute Lung Injury Model via the NLRP3 Inflammasome and TLR4/NF-κB Signaling Pathway via RHOB. *Int. J. Mol. Med.* **2019**, *43*, 1467–1477.
298. Ye, J.; Tang, X.; Li, M.; et al. MicroRNA-223 Alleviates Inflammatory Response in Renal Ischemia-Reperfusion Injury by Targeting NLRP3. *Kaohsiung J. Med. Sci.* **2024**, *40*, 789–800.
299. Neudecker, V.; Haneklaus, M.; Jensen, O.; et al. Myeloid-Derived miR-223 Regulates Intestinal Inflammation via Repression of the NLRP3 Inflammasome. *J. Exp. Med.* **2017**, *214*, 1737–1752.
300. Ye, D.; Zhang, T.; Lou, G.; et al. Role of miR-223 in the Pathophysiology of Liver Diseases. *Exp. Mol. Med.* **2018**, *50*, 1–12.
301. Wang, D.; Sun, S.; Xue, Y.; et al. MicroRNA-223 Negatively Regulates LPS-Induced Inflammatory Responses by Targeting NLRP3 in Human Dental Pulp Fibroblasts. *Int. Endod. J.* **2020**, *54*, 241–254.
302. Tian, J.; Zhou, D.; Xiang, L.; et al. miR-223-3p Inhibits Inflammation and Pyroptosis in Monosodium Urate-Induced Rats and Fibroblast-Like Synoviocytes by Targeting NLRP3. *Clin. Exp. Immunol.* **2021**, *204*, 396–

410.
303. Haque, M.M.; Yerex, K.; Kelekis-Cholakis, A.; et al. Advances in Novel Therapeutic Approaches for Periodontal Diseases. *BMC Oral Health* **2022**, *22*, 492.
304. Hua, F.; Tang, H.; Wang, J.; et al. TAK-242, an Antagonist for Toll-Like Receptor 4, Protects Against Acute Cerebral Ischemia/Reperfusion Injury in Mice. *J. Cereb. Blood Flow Metab.* **2015**, *35*, 536–542.
305. Liu, Z.; He, Y.; Xu, C.; et al. The Role of PHF8 and TLR4 in Osteogenic Differentiation of Periodontal Ligament Cells in Inflammatory Environment. *J. Periodontol.* **2021**, *92*, 1049–1059.
306. Clark, R.B.; Cervantes, J.L.; Maciejewski, M.W.; et al. Serine Lipids of Porphyromonas gingivalis Are Human and Mouse Toll-Like Receptor 2 Ligands. *Infect. Immun.* **2013**, *81*, 3479–3489.
307. Piao, W.; Song, C.; Chen, H.; et al. Endotoxin Tolerance Dysregulates MyD88- and Toll/IL-1R Domain-Containing Adapter Inducing IFN-β-Dependent Pathways and Increases Expression of Negative Regulators of TLR Signaling. *J. Leukoc. Biol.* **2009**, *86*, 863–875.
308. Matsuguchi, T.; Masuda, A.; Sugimoto, K.; et al. JNK-Interacting Protein 3 Associates with Toll-Like Receptor 4 and Is Involved in LPS-Mediated JNK Activation. *EMBO J.* **2003**, *22*, 4455–4464.
309. Hajishengallis, G.; Wang, M.; Bagby, G.J.; et al. Importance of TLR2 in Early Innate Immune Response to Acute Pulmonary Infection with Porphyromonas gingivalis in Mice. *J. Immunol.* **2008**, *181*, 4141–4149.
310. Makkawi, H.; Hoch, S.; Burns, E.; et al. Porphyromonas gingivalis Stimulates TLR2-PI3K Signaling to Escape Immune Clearance and Induce Bone Resorption Independently of MyD88. *Front. Cell. Infect. Microbiol.* **2017**, *7*, 359.
311. Finamore, A.; Roselli, M.; Imbinto, A.; et al. Lactobacillus amylovorus Inhibits the TLR4 Inflammatory Signaling Triggered by Enterotoxigenic Escherichia coli via Modulation of the Negative Regulators and Involvement of TLR2 in Intestinal Caco-2 Cells and Pig Explants. *PLoS One* **2014**, *9*, e94891.
312. Kanmani, P.; Ansari, A.; Villena, J.; et al. Immunobiotics Beneficially Modulate TLR4 Signaling Triggered by Lipopolysaccharide and Reduce Hepatic Steatosis in Vitro. *J. Immunol. Res.* **2019**, *2019*, 3876896.
313. Lysakova-Devine, T.; Keogh, B.; Harrington, B.; et al. Viral Inhibitory Peptide of TLR4, a Peptide Derived from Vaccinia Protein A46, Specifically Inhibits TLR4 by Directly Targeting MyD88 Adaptor-like and TRIF-related Adaptor Molecule. *J. Immunol.* **2010**, *185*, 4261–4271.
314. Rangasamy, S.B.; Jana, M.; Roy, A.; et al. Selective Disruption of TLR2-MyD88 Interaction Inhibits Inflammation and Attenuates Alzheimer's Pathology. *J. Clin. Invest.* **2018**, *128*, 4297–4312.
315. Kwon, H.K.; Patra, M.C.; Shin, H.J.; et al. A Cell-Penetrating Peptide Blocks Toll-like Receptor-Mediated Downstream Signaling and Ameliorates Autoimmune and Inflammatory Diseases in Mice. *Exp. Mol. Med.* **2019**, *51*, 1–19.
316. Zhou, X.; Li, X.; Wang, X.; et al. Cecropin B Represses CYP3A29 Expression through Activation of the TLR2/4-NF-κB/PXR Signaling Pathway. *Sci. Rep.* **2016**, *6*, 27876.
317. Toshchakov, V.Y.; Javmen, A. Targeting the TLR Signalosome with TIR Domain-Derived Cell-Permeable Decoy Peptides: The Current State and Perspectives. *Innate Immun.* **2020**, *26*, 35–47.
318. Takeshita, F.; Leifer, C.A.; Gursel, I.; et al. Cutting Edge: Role of Toll-like Receptor 9 in CpG DNA-Induced Activation of Human Cells. *J. Immunol.* **2001**, *167*, 3555–3558.
319. Bai, G.; Yu, H.; Guan, X.; et al. CpG Immunostimulatory Oligodeoxynucleotide 1826 as a Novel Nasal ODN Adjuvant Enhanced the Protective Efficacy of the Periodontitis Gene Vaccine in a Periodontitis Model in SD Rats. *BMC Oral Health* **2021**, *21*, 403.
320. Wang, N.; Xia, D. Activation of Local Innate Immune Signal Induces Periodontitis in Microbiota-Dependent Manner. *FEMS Microbiol. Lett.* **2019**, *366*, fnz147.
321. Hsieh, Y.C.; Lee, K.C.; Wu, P.S.; et al. Eritoran Attenuates Hepatic Inflammation and Fibrosis in Mice with Chronic Liver Injury. *Cells* **2021**, *10*, 1562.
322. Mattke, J.; Darden, C.M.; Vasu, S.; et al. Inhibition of Toll-like Receptor 4 Using Small Molecule, TAK-242, Protects Islets from Innate Immune Responses. *Cells* **2024**, *13*, 416.
323. Panaro, M.A.; Corrado, A.; Benameur, T.; et al. The Emerging Role of Curcumin in the Modulation of TLR-4 Signaling Pathway: Focus on Neuroprotective and Anti-Rheumatic Properties. *Int. J. Mol. Sci.* **2020**, *21*, 2299.
324. Yuan, T.; Tang, H.; Xu, X.; et al. Inflammation Conditional Genome Editing Mediated by the CRISPR-Cas9 System. *iScience* **2023**, *26*, 106872.
325. Collotta, D.; Bertocchi, I.; Chiapello, E.; et al. Antisense Oligonucleotides: A Novel Frontier in Pharmacological Strategy. *Front. Pharmacol.* **2023**, *14*, 1304342.
326. Tong, L.; Zhang, X.; Hao, H.; et al. Lactobacillus rhamnosus GG Derived Extracellular Vesicles Modulate Gut Microbiota and Attenuate Inflammation in DSS-Induced Colitis Mice. *Nutrients* **2021**, *13*, 3319.

327. Ohland, C.L.; MacNaughton, W.K. Probiotic Bacteria and Intestinal Epithelial Barrier Function. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2010**, *298*, G807–G819.
328. Kayesh, M.E.H.; Kohara, M.; Tsukiyama-Kohara, K. TLR Agonists as Vaccine Adjuvants in the Prevention of Viral Infections: An Overview. *Front. Microbiol.* **2023**, *14*, 1249718.
329. Zhang, J.; Chen, B.; Gan, C.; et al. A Comprehensive Review of Small Interfering RNAs (siRNAs): Mechanism, Therapeutic Targets, and Delivery Strategies for Cancer Therapy. *Int. J. Nanomedicine* **2023**, *18*, 7605–7635.
330. Lim, Y.; Kang, T.K.; Kim, M.I.; et al. Massively Parallel Screening of Toll/Interleukin-1 Receptor (TIR)-Derived Peptides Reveals Multiple Toll-like Receptors (TLRs)-Targeting Immunomodulatory Peptides. *Adv. Sci.* **2025**, *12*, e2406018.
331. Gümüş, P. The Role of TLRs in the Pathogenesis of Periodontal Diseases. *J. Dent. Sci. Ther.* **2016**, *1*, 3–6.
332. Fatemi, K.; Radvar, M.; Rezaee, S.A.; et al. Comparison of Relative TLR-2 and TLR-4 Expression Level of Diseased and Healthy Gingival Tissue of Smoking and Non-Smoking Patients and Periodontally Healthy Control Patients. *Aust. Dent. J.* **2013**, *58*, 315–320.
333. Singh, S.; Mishra, A. Revisiting the Significance of TLRs: Current Understanding and Future Scope for Therapeutic Implications. *Curr. Signal Transduct. Ther.* **2025**, *20*, E15743624341069.
334. Slivka, P.F.; Shridhar, M.; Lee, G.I.; et al. A Peptide Antagonist of the TLR4–MD2 Interaction. *Chembiochem* **2009**, *10*, 645–649.
335. Piao, W.; Vogel, S.N.; Toshchakov, V.Y. Inhibition of TLR4 Signaling by TRAM-Derived Decoy Peptides In Vitro and In Vivo. *J. Immunol.* **2013**, *190*, 2263–2272.
336. Feng, W.; Yu, H.; Xue, T.; et al. The Biocomplex Assembled from Antigen Peptide and Toll-like Receptor Agonist Improved the Immunity against Pancreatic Adenocarcinoma In Vivo. *J. Oncol.* **2022**, *2022*, 2965496.