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REVIEW ARTICLE

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Toll-like receptors and *Streptococcus mutans*: An updated review article

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Abstract
It has been reported that toll-like receptors (TLRs) are the main innate immune receptors that recognize gram-positive pathogen-associated molecular patterns (PAMPs). The molecules can induce expression of the innate immune-related molecules that are essential against the bacteria. *Streptococcus mutans* (*S. mutans*) is a potential caries-associated pathogen, and innate immunity plays a key role in inhibiting its development and the progression of inflammatory responses. Recently, the roles played by TLRs against *S. mutans* and the induction of inflammatory responses were evaluated by several investigations. This review article discusses updated information regarding the roles played by TLRs and their potential therapeutic effects against *S. mutans*.

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Introduction

It has been reported that several bacteria are resident in the human oral cavity that are responsible for dental caries and dental pulp infections.[1] Among them, *Streptococcus mutans* (*S. mutans*) is the famous bacterium, which is under more investigation. *S. mutans* was discovered by J. Clarke more than 100 years ago.[2] Due to its ability to synthesize huge quantities of extracellular glucan polymers, transport or metabolize a wide range of carbohydrates, and thrive under environmental stress conditions, such as low pH, it has been considered a potential caries-associated pathogen. S. *mutans* is the main organism that alters the microenvironment via forming an extracellular polysaccharide (EPS)-rich and low pH milieu to create a favorable niche for other microorganisms.[3] The bacterium is implicated in other human-related disorders, including subacute bacterial endocarditis.[4] S. *mutans* is classified into four serological groups, including c, e, f, and k, due to the composition of cell-surface rhamnose–glucose polysaccharide.[5] *S. mutans* has some genotypes that are associated with great variations in the phenotypes directly related to virulence, such as the ability to form biofilm.[6] In addition to genetic factors, it seems that epigenetic factors, such as small noncoding RNAs, play key roles in the ability of biofilm formation by *S. mutans*.[7] Therefore, it appears that, although immune responses to each serotype may be different, the potential abilities of the various genotypes can also be associated with altered immune responses to *S. mutans*.

Additionally, *S. mutans* plays critical roles in other human-related disorders, such as septic shock, acute pansinusitis, periapical abscess, ulcerative colitis, gingival recession (retraction of gum tissue), bleeding gums, periodontal diseases, and tooth pulp.[8] Due to the wide range of pathogenicity of *S. mutans*, it seems that the bacterium has a huge range of interaction with immune responses.

It has been reported that innate immunity plays a critical role against gram-positive bacteria.[9] Accordingly, the molecules involved in the innate immune responses against gram-positive bacteria can be considered as the main factors against *S. mutans*.[10] It has been reposted that toll-like receptors (TLRs) are the main pathogen recognition receptors that are expressed either on the cell membrane or intracytoplasmic vesicles.[11-13] TLRs are categorized into a family comprising 13 members, while TLR1 to TLR10 are expressed in humans only.[14] The molecules are expressed in dimmer format, including heterodimers of TLR1/TLR2 and TLR6/TLR2, and homodimers of TLR2/TLR2, TLR3/TLR3, TLR4/TLR4, TLR5/TLR5, TLR7/TLR7, TLR8/TLR8, and TLR9/TLR9.[14,15] The molecules recognize several molecules and activate the innate immune responses.[16,17] For example, the main ligands for TLR1/TLR2, TLR6/TLR2, TLR2/TLR2, TLR3/TLR3, TLR4/TLR4, TLR5/TLR5, TLR7/TLR7, TLR8/TLR8, and TLR9/TLR9 are bacterial lipopeptides, bacterial lipopeptides, bacterial peptidoglycan, double-stranded RNA, lipopolysaccharide, bacterial flagellin, single-stranded RNA, single-stranded RNA, and CPG DNA, respectively.[16] However, TLRs use several intracellular signaling pathways to induce transcription from immune-related genes in innate immune cells.[16] For example, TLR3/TLR3 homodimer uses TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent signaling pathways,[17,18] while TLR4/TLR4 homodimer uses both TRIF and myeloid differentiation primary response 88 (MYD88)-dependent pathways.[19] Other TLRs use the MyD88-dependent pathway only.[14] The pathway activations result in the activation of some transcription factors, which are the molecules responsible for transcription from innate immunity-related genes. Accordingly, some transcription factors, such as nuclear factor kappa light chain enhancer of activated B cells (NF-κB), activator protein 1 (AP-1), and interferon regulatory factor 3 (IRF3), are important factors for transcription from the genes.[20] Cytokines, pro-inflammatory molecules, adhesion molecules, and the major histocompatibility complex (MHC) are the main molecules that are expressed following activation of TLRs.[21] The immune-related molecules play a key role against gram-positive bacteria. Hence, due to the various ranges of the ligands that are recognized by TLRs and their important roles against gram-positive bacteria, it has been hypothesized that these molecules play a key role against *S. mutans*.

Toll-like receptors play a key role in the induction of inflammation in the dental pulps and gums in response to *Streptococcus mutans*

Previous investigations have proved that TLRs are expressed on the resident dental pulp cells, including normal human odontoblasts, dental pulp tissue, dental pulp stem cells (DPSCs), and immune cells.[22] In addition, DPSCs can be considered as an important part of the innate immune response against *S. mutans*.[22] Previous investigations have revealed that *S. mutans* significantly activates DPSCs via interactions with TLR4.[23,24] In another words, DPSCs can recognize and respond to *S. mutans* via TLR4. Therefore, it seems that TLRs are the main receptors for non-immunologic cells to develop into dental pulp normally. However, these molecules are the main immune cell receptors that are resident in the tissue. Accordingly, the receptors may either participate in the induction of immune responses against *S. mutans* to inhibit its growth or in the induction of inflammation and then tissue damage. In agreement with the hypothesis, it has been reported that the lipoteichoic acid of *S. mutans* interacts with TLR2 and induces inflammatory mediators in murine macrophages, including the production of tumor necrosis factor-alpha (TNF-α) and nitric oxide (NO) in a dose-dependent manner.[25] The inflammatory roles played by TLR2 in the recognition of *S. mutans* and production of interleukin-6 (IL-6), IL-8, and monocyte chemoattractant protein-1 (MCP-1) have been demonstrated in another *vitro* study.[26] Additional investigations also confirmed the roles played by TLRs against *S. mutans* through an *in vivo* investigation.[27,28] They reported that TLRs are the main inducers of inflammation in the dental pulp tissues via recognition of *S. mutans*-related ligands.[27,28] The pro-inflammatory roles played by TLRs against *S. mutans* and the induction of some pro-inflammatory diseases, such as periodontitis, have also been documented by Yoshioka et al.[29] Animal models revealed that *S. mutans* is the microorganism responsible for the induction of balloon angioplasty (BA) injury via upregulation of TLR4.[30] Hajishengallis et al. reported that *S. mutans*

protein AgI/II is the primary molecule for cytokine release during atherosclerotic disease in dependent of CD14 and TLR4.[31] To confirm the pro-inflammatory roles of *S. mutans* via interactions with TLRs, Horst et al. reported that transforming growth factor-beta1 (TGF-B1) is a main factor for regulation of pro-inflammatory reactions in odontoblasts against *S. mutans* via down-regulation of TLR2 and TLR4.[32]

Due to the results reported previously, it appears that TLRs are the main components in the inflammation together with *S. mutans*. In another words, the main cause of several pro-inflammatory-related gum and dental disorders may be the interaction of *S. mutans* antigens with TLRs. Accordingly, using some TLR antagonists may be considered as future immunotherapies against gum and dental inflammations. Figure 1 illustrates the main roles played by TLRs in the induction of inflammation following infection by *S. mutans*.

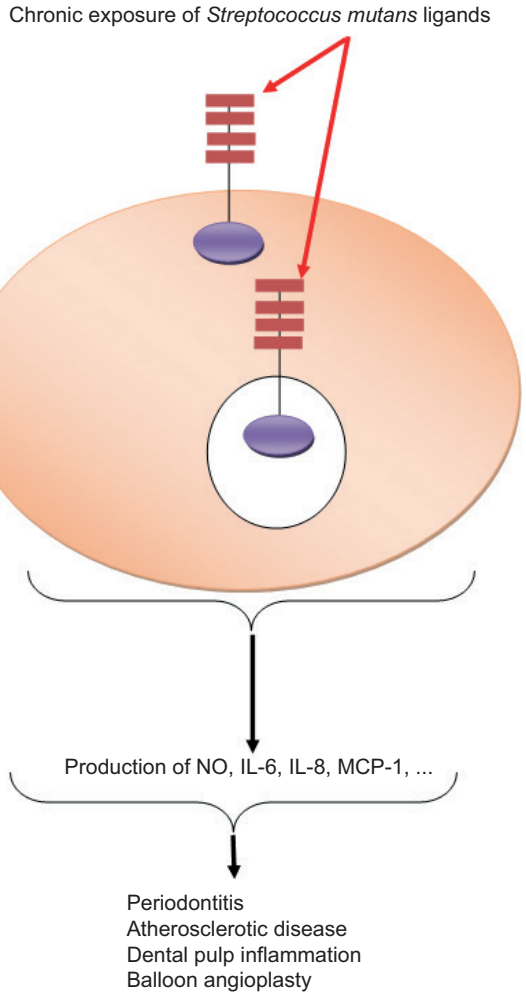

Figure 1 The roles played by TLRs in the induction of inflammation during chronic inflammation with *Streptococcus mutans*. The figure illustrates that chronic exposure of *S. mutans* antigens to both cell surface and intra-vesicular TLRs can be associated with expression of pro-inflammatory molecules, which the main responsible factors for inflammation induction and its-related disorders.

Toll-like receptors are the main receptors for protection against *Streptococcus mutans*

The protective roles played by TLRs against *S. mutans* have also been documented previously. For example, it has been demonstrated that Pam3CSK4 and monophosphoryl lipid A are the important synthetic ligands for TLR1/TLR2 heterodimer and TLR4/TLR4 homodimer, respectively.[33] Accordingly, using the ligands as adjuvants significantly increased the immune responses against recombinant proteins of *S. mutans*.[34] Additionally, the recombinant saliva-binding region (SBR) of *S. mutans* can induce the production of mucosal IgA in a TLR2, TLR4, and MyD88-dependent manner.[35] It has been demonstrated that the Myd88 signaling pathway includes interleukin-1 receptor-associated kinase 4 (IRAK4), IRAK1, tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6), and finally activations of some transcription factors, such as IRFs, NF-κB, and AP-1.[16,17] The transcription factors are the molecules responsible for induction of inflammation following the recognition of *S. mutans* antigens by TLRs. Figure 2 illustrates the signaling pathways that lead to the induction of inflammation by *S. mutans* in dependent of TLRs. Xu et al. also confirmed the results and revealed that saliva-binding region (SBR) of *S. mutans* antigen can activate dendritic cells via interactions with TLR4.[36] Interestingly, the study demonstrated that activation of mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase 1/2 (ERK), c-Jun NH2-terminal kinase (JNK), and p38, by TLR4, is responsible for the activation of dendritic cells by intracellular signaling molecules.[36] The critical roles played by TLRs against *S. mutans* have also been proven by several investigations. Conti et al. reported that using herbal drugs that are associated with increased expression of TLRs and their related transcription factors, such as NF-κB, can increase immune responses against *S. mutans*.[37] Another investigation revealed that following the interaction of TLR2 with the antigens *S. mutans*, human odontoblast-like cells produce NO with antibacterial activity.[38] Hong et al. also confirmed the roles played by TLR2 against *S. mutans*.[39] They revealed that lipoteichoic acid in *S. mutans* is the main ligand for activation of TLR2 signaling pathways.[39] The critical roles played by TLR2 against *S. mutans* have also been demonstrated by Japanese investigators.[40] *S. mutans* wall-associated protein A is another ligand that promotes TLR4-induced dendritic cell (DC) maturation and functions.[41] Accordingly, the protein induces maturation of DCs via the NF-κB and MAPK signaling pathways and then upregulation of CD80/86, CD40, major histocompatibility (MHC) II, IL-12, IL-6, and TNF-α by the cells.[41] An in vitro study revealed that *S. mutans* stimulates TLR2 and TLR4 receptors, which are associated with the activations of ERK/p38/JNK and NF-κB, respectively.[42] Thus, it appears that *S. mutans* stimulates TLRs in various signaling pathways. In addition to the direct interaction of *S. mutans* antigens with TLRs, conjugation of *S. mutans* antigens with other TLR ligands can increase immune responses against the bacterium. For instance, Sun et al. showed that conjugation of *E. coli* flagellin and *S. mutans* PAc significantly interacts with the TLR5/TLR5 homodimer and increases the efficacy of the anti-caries mucosal vaccine.[43]

The potential roles played by TLR3 in inducing of humoral immunity against *S. mutans* have also been demonstrated by Nakamura et al.[44] Interestingly, some investigations revealed that although TLRs are not responsible for the detection of *S. mutans* proteins in some cases, the cross-talks between intracellular signaling, such as focal adhesion kinase (FAK) and MyD88, can be considered as the main phenomenon for induction of inflammation and immune responses against *S. mutans*.[45] Similarly, Semaan et al. showed that Etk/BMX, a Btk family tyrosine kinase, and Mal are the main linkers for cross-talk between MyD88 and FAK pathways.[46] It has also been demonstrated that TLRs are the molecules responsible for producing phospholipase A2 and platelet activation factor (PAF), via recognition of *S. mutans* PAMPs, and activation of inflammation.[47] Therefore, it appears that TLRs and their signaling pathways can also participate against *S. mutans*, either directly or indirectly. The molecular mechanisms used by TLRs in the pathogenesis of *S. mutans* are illustrated in Figure 2.

Collectively, it seems that TLRs are the main parts of immune response puzzles against *S. mutans*. Due to the important roles played by the molecules against the bacterium, their ligands may be considered as potential adjuvants in the future vaccines to control the cariogenic bacterium.

Toll-like receptors may suppress the immune system in response to *Streptococcus mutans*

Although TLRs are the main inducers of immune responses against *S. mutans*, some investigations revealed that the bacterium uses some TLRs to induce immune tolerance against its antigens. For example, Saeki et al. reported that *S. mutans* interacts with TLR2 to develop of regulatory T lymphocytes.[48] Another investigation by Park et al. revealed that *S. mutans* antigens can induce apoptosis in immune cells via interactions with TLRs in a dose-dependent manner.[49] Additionally, it appears that coinfection with other pathogenic or opportunistic bacteria may be a critical factor in altering the effects of *S. mutans* on immune cell functions. For example, Zhang et al. reported that during coinfection, *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*), but not *S. mutans*, significantly participated in the induction of TLRs-mediated inflammation and the production of atherosclerotic plaque in animal models.[50] TLR9 is another candidate to regulate

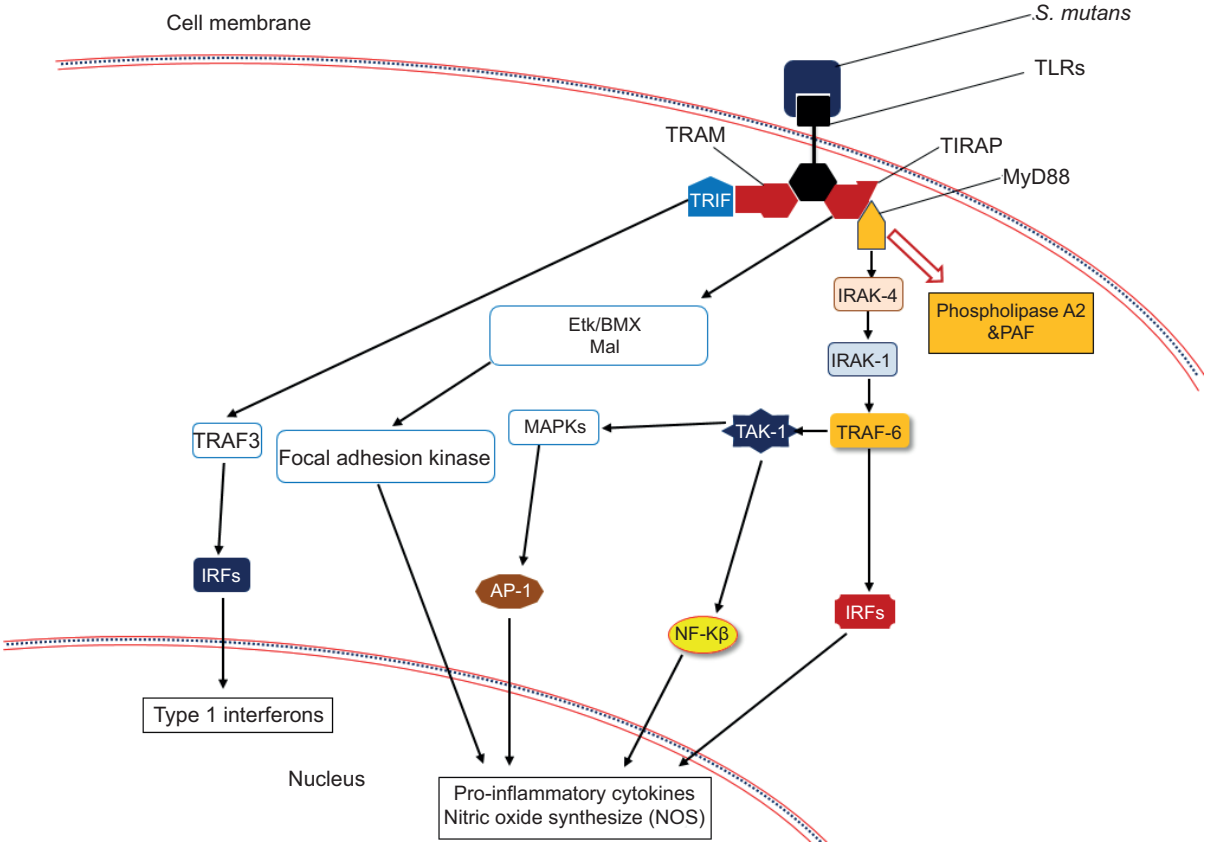

Figure 2 The molecular mechanisms used by TLRs in the pathogenesis of *S. mutans*. TLRs use Myd88 and TRIF-dependent pathways to activate transcription factors to transcript from pro-inflammatory cytokines, and nitric oxide synthesize (NOS) and type 1 interferons. TLRs also induce the production of phospholipase A2 and PAF to induce inflammation in dependent of *S. mutans*.

immune responses against *S. mutans* via recognition of periodontal bacterial DNA.[51]

Conclusion

Collectively, it appears that TLRs are the main innate immunity receptors that participate in the induction of immune responses against *S. mutans*. However, it may be hypothesized that the doses of *S. mutans* antigens, the immune cell target, coinfection with other pathogenic or opportunistic bacteria, and the type of TLRs, for example, TLR9, are the main factors that determine the outcome of immune responses against *S. mutans*. Additionally, as mentioned previously, it appears that *S. mutans* stimulates different signaling pathways depending of the TLR type. The main factors that determine the protective or pro-inflammatory roles played by TLRs against *S. mutans* are yet to be clarified. However, the authors propose that genetic and epigenetic factors are the critical factors in determining the outcome of the infection. Additionally, due to the fact that the infection with *S. mutans* is a chronic form of the bacterial infection, immunological exhaustion may be a main factor in the induction of pathological inflammation in the dental pulps and gums of the teeth. Due to the critical roles played by TLRs against *S. mutans*, it seems that using TLR ligands as adjuvants in association with *S. mutans* antigens can be considered for designing vaccines against the bacterium. However, the majority investigations were performed on two main TLRs, TLR2 and TLR4. So, future investigations need to be directed at using the ligands for other TLRs.

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