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The Role of TLRs in the Pathogenesis of Periodontal Diseases

Pınar Gumus DDS, PhD

Department of Periodontology, School of Dentistry, Ege University

***Corresponding author:** Pınar Gumus DDS, PhD, Department of Periodontology, School of Dentistry, Ege University, Izmir, Turkey; E mail: gumuspinar@yahoo.com

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Abstract

Periodontitis is a complex and multi-factorial inflammatory disease. Dysbiotic microbial communities of keystone pathogens induce host response, which are also responsible for tissue-destructive inflammation and inflammatory bone loss. Microbiata in the microbial dental biofilm stimulate innate immunity via the Toll-like receptor (TLR) family of pattern-recognition receptors. TLRs recognize the antigens and activate pro-inflammatory cytokines in the periodontal tissues. The transition from gingivitis to periodontitis requires both a dysbioticmicrobiota and a susceptible host. Understanding the role of TLRs signaling in the periodontal health and disease may be helpful for providing new insight to the pathogenesis of periodontitis and developing new therapeutic approaches.

Keywords: Periodontal disease, Toll like receptors,Dysbiosis.

Introduction

Periodontal diseases are a group of infectious/inflammatory diseases involving Gram-negative, anaerobic and microaerophilic bacteria that colonize the subgingival area and cause local as well as systemic elevations of pro-inflammatory prostaglandins and cytokines, which result in tissue destruction. Periodontitis is characterized by gingival inflammation, alveolar bone resorption, and attachment loss [1].Immune responses are activated upon stimulation by bacteria or their toxins present in the dental biofilm and eventually play a major role in alveolar bone destruction observed in periodontitis. However, the exact mechanisms of the molecular recognition and signalling transduction of host immune-inflammatory responses in periodontitis remain obscure [2]. Moreover, mechanisms leading to dysbiosis in microbial dental biofilm in periodontitis or homeostasis in periodontal health have not been clarified yet.

What is Dysbiosis?

Dysbiosis is defined as an imbalance in the relative abundance of microbial species within an ecosystem that is associated with a disease such as periodontitis [3-5]. Dysbiosis can be either the cause or the consequence of disease. Homeostasis is a condition of equilibrium or stability in a system [4,5]. In homeostasis there is a balanced relation between a host tissue and the resident microbiota that prevents destructive inflammation or disease [4,5].

The mechanisms leading to dysbiosis have not been clarified so far. Some researchers try to explain the mechanism with the keystone-pathogen hypothesis that favor the remodeling of a normally symbiotic microbiota into a dysbiotic and disease-provoking state. Certain low-abundance pathogens can subvert host immunity in this way [3,6].

Keystone pathogens are microbial species that remodels a microbial community in ways that promote disease onset and progression [4,5]. Keystone pathogens can cause or contribute to homeostasis breakdown. Certain periodontal bacteria, such as *Treponemadenticola, Tannerella forsythia*, and *Aggregatibacteractinomycetemcomitans*are strongly associated with destructive inflammatory responses and additionally subvert the host response in that way.

What is the role of Dysbiosis in disease?

Impairment of homeostatic balance leads the destructive inflammation in periodontitis [7]. It has recently been proposed that periodontitis fundamentally represents disruption of host-microbial homeostasis caused by dysbiosis of the periodontal microbiota[7,8]. In a study it was shown that *P. gingivalis*can act as a keystone pathogen, which reshapes an otherwise harmless periodontal microbiota into a disease-provoking microbiota[7]. Moreover, *P. gingivalis*act as a keystone member of the periodontal microbiota because it has an ability to exploit complement and TLRs [7]. Subversion of complement and TLRs might contribute to periodontal tissue destruction. The interactions between microbiata and the host immune receptors may initiate the cytokine production and could be responsible for the tissue breakdown in inflammatory response.

What is TLR?

Toll gene products were first discovered in 1985 and were described as being critical for the embryonic development of

dorsal-ventral polarity in the fruit fly, Drosophila [9,10]. In 1991 the first TLR was identified in humans [11]. Now it is quite clear that Toll-like receptors function as key pattern-recognition receptors of the innate immune system [12]. They recognize and distinguish highly conserved structures present in large groups of microorganisms. The structures are referred to as pathogen-associated molecular patterns. TLRs are pattern recognition receptors (PRRs), which recognize signature molecules of microorganisms in innate immune systems [13].In addition to their regulation of innate immunity, a subset of TLR-induced signals is dedicated to the control of adaptive immunity [14]. TLRs are predominantly expressed on cells of the innate immune system, including neutrophils, monocytes/macrophages, and dendritic cells. Bacteria express various pathogen-associated molecular patterns (PAMPs) that can be detected by TLRs [15]. Two members of the TLR family, TLR2 and TLR4, have been identified as the principal signaling receptors for bacterial cell wall components. TLR2 recognizes a wide variety of PAMPs, such as lipoproteins and peptidoglycans from both Gram-positive and Gram-negative bacteria, as well as lipoteichoic acid from Gram-positive bacteria [16]. On the other hand, TLR4 recognizes lipopolysaccharide (LPS) from Gram-negative bacteria [17].

How TLRs activate cytokine production?

*Porphyromonasgingivalis*is a Gram-negative anaerobic bacterium implicated as a major periodontal pathogen [18,19]. Recent studies demonstrated that *P. gingivalis*orchestrates inflammation through manipulation of host immunity and periodontal microbiota and that periodontal disease is initiated by polymicrobial synergy and dysbiosis[3,20]. Surface components of *P. gingivalis*, such as LPS, lipoproteins, and fimbriae, interact with TLR2 and TLR4 expressed by host cells and stimulate production of proinflammatory cytokines [21]. They play a key role in host defense by recognizing, engulfing, and killing microorganisms [14]. Stimulation of TLRs by microbial components triggers expression of several genes that are involved in immune responses. The molecular mechanisms by which TLRs induce gene expression have different TLR-mediated signaling pathways [22].

Myeloid differentiation primary-response protein 88 (MyD88), a key adaptor molecule, is used by most TLRs. MyD88 mediates the TLR-signaling pathways [23]. TLR signaling cascades are separated into two groups: MyD88-dependent pathway and MyD88-independent pathway. MyD88-dependent pathway is essential for most TLR-mediated cell activation [24,25]. Activation of these pathways induces expression of cytokines and chemokines[23].

Where are TLRs in periodontal tissues?

TLR expression by human gingival epithelial cells has been investigated in gingival biopsies and the cells express TLR2, TLR6, and TLR9 [26] and low levels of TLR4 [27]. An abundance of TLR2-positive cells has been observed also in connective tissue subjacent to the pocket epithelium [28]. Gingival epithelial cells express TLR3 and TLR9 [26] and human gingival fibroblasts express TLR2, TLR4 and TLR9 [29,30].

How chronic periodontitis affects TLR activities?

Recently, TLR activities have become a popular topic in periodontitis because of the new data about dysbiotic microbial communities of keystone pathogens and the host reaction to microbiata. Most of the studies have shown elevated TLR activities in periodontitis and these activities positively correlated with the clinical periodontal parameters. Beklen*et al. (yıl)* studied ten healthy and ten periodontitis gingival tissue specimens and they observed that periodontitis samples showed more intense TLR4 expression on gingival epithelial cells [31]. In another study, authors found that the expression level of TLR2 was higher in all the periodontitis patients than in healthy individuals and the expression of TLR2 was higher in the epithelial cells than in the connective tissue cells [32]. Wara-aswapati examined the mRNA expression levels of TLR2, TLR4, and TLR9 and their relationship with periodontopathic bacteria in periodontal tissues. Furthermore, the mechanism of TLR induction by *Porphyromonasgingivalis*was investigated in human gingival fibroblasts. Gingival tissue and subgingival plaque samples were collected from 19 patients with chronic periodontitis and 16 control individuals without periodontitis. According to the results, the expression levels of TLR2 and TLR9 were significantly higher in the tissues of periodontitis patients compared to the tissues in the control group. The mRNA levels of TLR2 and TLR9, but not TLR4, were positively correlated with the number of *P. gingivalis*in subgingival plaque. This study suggests that *P. gingivalis*infection induces TLR2 and TLR9 upregulation in patients with periodontitis [33].Moreover,statistically significant upregulation of TLR9 and TLR8 have been reported in chronic periodontitis tissues compared to healthy sites [34]. In another study, gingival tissue samples were obtained from eight chronic periodontitis and nine gingivitis (3 mild; 3 moderate; 3 severe) patients. Eight control samples were also obtained from healthy individuals. The expression of TLR2 and TLR4 was significantly elevated in tissues of gingivitis and chronic periodontitis compared to the controls. In gingivitis samples TLR2 expression was increased compared to TLR4. The expression of TLR4 was significantly higher than TLR2 in chronic periodontitis [35]. Lappin*et al* showed that the median soluble stimulants of TLR2 and TLR4 were significantly higher in saliva of periodontitis patients compared with saliva of healthy subjects [36]. Budunel*et al* investigated whether patients with chronic periodontitis exhibit different salivary or plasma concentrations of TLR2 and TLR4 compared to subjects who are clinically healthy [37]. Twenty-two otherwise healthy patients with chronic periodontitis and 21 systemically and periodontally healthy control subjects were included in that study. The salivary TLR2 levels were similar in the two study groups. The patients with chronic periodontitis exhibited significantly higher salivary TLR4 and plasma TLR2 and TLR4 levels [37]. In a recent study, subgingival plaque samples from both healthy and diseased sites in the same individuals were obtained from adults with chronic periodontitis and screened for their ability to either activate TLR2 or TLR4 and to antagonize TLR4-specific activation agonist, *F. nucleatum*LPS. Subgingival plaque from diseased sites strongly activated TLR4, while matched plaque samples obtained from healthy sites were significantly more variable with some samples displaying strong TLR4 antagonism while others were strong TLR4 agonists when combined with *F. nucleatum*LPS [38].Wang *et al* found increased expression of TLR-2 in human gingival fibroblasts of inflammatory gingiva than those in healthy group [39]. Mori *et al* investigated the expression of TLR2 and TLR4 in human periodontal disease and showed higher TLR2 positive cells in mild group and higher TLR4 positive cells in severe gingivitis [40].

Conclusion

In summary, periodontitis is a complex and multi-factorial inflammatory disease. Immune response does not act solely as a protective mechanism, but it is also responsible for tissue breakdown in periodontal diseases. Periodontal tissue homeostasis in regards with the balance between the host response and themicrobial challenge in health and the mechanisms in controlled inflammatory state in gingivitis has not been clarified yet. The transition from gingivitis to periodontitis requires both a dysbioticmicrobiota and a susceptible host. Understanding the role of TLRs signaling in the periodontal health and disease should be helpful for providing new insight to the pathogenesis of the periodontitis and new therapeutic approaches may be developed.

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