Role of DKK1 in Periodontitis and Innovative Strategy with its Neutralizing Antibody for Periodontitis Treatment

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Abstract

As host response can be hard to predict due to the complexity of pathogens in periodontitis, the efforts of work on etiology of periodontitis to eliminate inflammation seems complicated. To relieve bone resorption and prevent tooth loss eventually, we investigate the mechanism of bone homeostasis and target at the role of DKK1 in periodontitis. With abundance of evidence, we have the hypothesis that TNFα could induce high expression of DKK1, then block Wnt/β-catenin pathway, resulting in bone resorption even tooth loss in periodontitis. Anti-DDK1 antibody could reverse the damage and serve as an assisting therapy to relieve bone loss. If this hypothesis is clarified in the future, plenty of patients suffered from periodontitis will benefit from this antibody-mediated treatment.

Introduction

Periodontitis is a prevalent inflammation-induced disease. It can cause periodontal destruction and alveolar bone resorption, leading to tooth loss eventually (Figure 1A). So far, periodontitis still remains the most common cause of tooth loss in the world [1]. And it can induce systematic problems as vascular endothelial dysfunction [2]. Thus, exploring an effective way to conquer this disease will be quite beneficial. Periodontitis is an infectious disease involving a complex interaction between the oral microorganisms organized in a biofilm structure and the host immune response [1]. There can be an innate-only response, whilst others will need to invoke the inflammatory response and yet others will require the adaptive immune response to reduce or remove the microbial challenge [3]. And host response can be hard to predict due to the complexity of pathogens.

The most widely used treatment is physically removing the pathogenic bacterial-plaque biofilm by debridement, which appears as the gold standard for the treatment of inflammatory periodontitis for now [4,5]. However, it cannot fundamentally avoid inflammation relapse, because bacterial-plaque will always reattach, and stimulate inflammatory cascade constantly, especially for those patients with poor oral hygiene [6]. Conventional drug treatments, such as anti-inflammatory agents, have limited effects on reversing bone resorption, which is the crucial factor for tooth loss [7]. As new pathogens are suspected in the onset and progression of periodontitis, much more efforts of developing antibodies for new pathogens are suspected in the onset and progression of periodontitis, much more efforts of developing antibodies for new pathogens in biofilm are expected [1]. In light of this, therapies that specifically target on bone turnover should be investigated and may serve as an assisting therapy.

A main hallmark of periodontitis pathogenesis is the imbalance of the osteoblast-osteoclast axis that is driven by periodontal inflammation, resulting in evident bone resorption by osteoclasts [8]. Wnt/β-catenin pathway is a key signaling for bone metabolism [9-13]. It promotes the differentiation of progenitor cells into osteoblasts to increase bone formation [14] and decrease bone resorption by reducing osteoclastogenesis [15-17]. As a member of Dickkopf (DKK) family, DKK1 is a natural inhibitor of Wnt/β-catenin pathway [18-21]. DKK1 expression can influence bone homeostasis and result in systematic bone diseases [22-25].

In periodontitis, inflammation uncouples bone formation from bone resorption via inflammatory mediators [26]. These mediators are able to induce the cascade of molecular events associated with extracellular matrix degradation and resultant tissue damage [7]. Among numerous inflammatory mediators, tumor necrosis factor-alpha (TNFα), a critical pro-inflammatory cytokine [27,28] contributes significantly to the pathologic bone loss in periodontitis [26,29]. It is produced by activated macrophages as well as by many other connective tissue cells, such as synoviocytes and periodontal fibroblasts [7]. TNFα has been reported to act either directly on osteoclasts [30] or indirectly to induce osteoclast formation through the stimulation of RANKL production by osteoblasts [31].

Potential key role of DKK1 in the process of periodontitis

It has been reported that DKK1 appears to actively participate in joint remodeling in arthritis [22,32]. Similar with periodontitis, inflammation-induced bone loss occurs in rheumatoid arthritis (RA). Inflammatory aspect causes destruction of joints and induces lytic lesions in the peri-articular bone which is not adequately repaired by bone coupling [33].

Diarra et al. found that DKK1 protein expression was enhanced in synovial fibroblasts and increased in the serum of patients with RA compared with healthy controls. Furthermore, its expression could be induced by TNFα, while the blockade of DKK1 could reverse TNFα inhibitory effect on bone formation [32]. Using the anti-DDK1 antibody in human TNF transgenic (hTNFtg) mice not only led to a complete inhibition of bone erosions, but also promoted osteophyte formation in
sites prone to structural damage [32,34]. And the molecular mechanism of this new bone formation was associated with activation of the Wnt/β-catenin pathway [32].

Recently, evidence has been raised that the mRNA and protein levels of DKK1 were significantly increased in the gingival tissues of the chronic periodontitis when compared to the non-periodontitis group [35]. The induction of DKK1 by TNFα has been linked to increased bone loss in a mouse model of inflammatory arthritis and in human rheumatoid arthritis [33], supporting the present finding of the overexpression of TNFα in gingival tissue of periodontitis individuals. However, the data on the cellular and molecular mechanisms responsible for the increased levels of DKK1 in periodontal tissues is not provided [35]. A single study showed that the pharmacologic inhibition of SOST, another antagonist of Wnt/β-catenin pathway, restored the alveolar bone destruction following experimental periodontitis in rats by using a SOST neutralizing monoclonal antibody [36]. Interestingly, Blockade of DKK1 not only prevented impaired osteoblastogenesis, but also counteracted TNF-mediated SOST expression in differentiated osteoblasts in vitro and in vivo [35].

However, few researches involve promising therapeutic target of blocking DKK1. Given the critical role of TNFα in periodontitis, its ability to up-regulate expression of DKK1 in RA, and the high level of DKK1 expression in periodontitis, we propose that bone loss in periodontitis may partially due to downregulation of Wnt/β-catenin pathway by TNF-induced DKK1 overexpression (Figure 1B).

**Innovative strategy with anti-DKK1 antibody for periodontitis treatment**

One of the most interesting results from RA researches is that the “bone protective” effect by using anti-DKK1 antibody was achieved without altering the clinical signs of inflammation, indicating a uncoupling of inflammation and joint destruction. This directly inspires us to suppose that anti-DKK1 antibody may be a very promising agent for periodontitis treatment (Figure 1C).

Although periodontitis is a bacterially induced inflammatory disease [4], bacterial-plaque will always reattach after physical treatment, and stimulate inflammatory cascade constantly. On the other hand, once the inflammation occurs, numerous mediators and signaling molecules are involved in its development. However, the neutralization of DKK1 can protect bone and enhance new bone formation without altering the clinical signs of inflammation [32]. In other words, anti-DKK1 antibody can promote bone regeneration even if the inflammation cannot be eradicated entirely. This capacity undoubtedly has great value in periodontitis treatment.

**Conclusion and Perspective**

Integrated by evidence of role of Wnt/β-catenin pathway in bone physiology, induction of DKK1 by TNFα in RA and high expression of DKK1 in chronic periodontitis, we come to the hypothesis that TNFα can induce DKK1 to block Wnt/β-catenin pathway, resulting in bone loss in periodontitis. Based on this, we propose that specific anti-DKK1 antibody could serve as assisting therapy to prevent bone loss as well as systematic dysfunction caused by periodontitis.

Developing anti-DKK1 antibody provides us with a new direction to cure periodontitis. However, the cellular and molecular mechanism responsible for high level of DKK1 expression in periodontal tissues still remains unknown. In inflammatory environment, downregulation of the levels Wnt/β-catenin by treatment with DKK1 leads to activation of the noncanonical Wnt/Ca2+ pathway, resulting in the promotion of osteogenic differentiation in periodontal ligament stem cells (PDLSCs), which means that PDLSCs’ ability of bone regeneration is awakened in inflammatory environment [37]. It seems DKK1-induced noncanonical Wnt pathway contributes...
to relieve bone resorption indirectly, which is totally the opposite conclusion compared with above. It indicates that more details associating with DKK1 in the periodontal tissue remain to be discovered. The relationship between DKK1 and other molecules, cells and signaling pathways could be far more complicated beyond present knowledge. This hypothesis need to be clarified more thoroughly and deeply before it is used clinically.

References

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Conflicts of inte est statement

None declared.

Acknowledgement

Gratitude to the National Natural Science Foundation of China ((NO. 81371711, 81371172)).