Sprouty2 Inhibition Resolves Inflammation in Periodontal Disease and Creates a Suitable Environment for Periodontal Tissue Regeneration

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Abstract

Introduction: Periodontitis, a bacterial infection affecting periodontal tissues, results in the alveolar bone destruction. In particular, periodontitis is associated with Porphyromonas gingivalis (Pg)-induced inflammation and an increase of macrophages infiltrated into the gingiva. Sprouty (Spry) proteins function as negative regulators, which interfere with the activation of fibroblast growth factor (FGF) pathway by suppressing the mitogen-activated protein kinase (MAPK) signaling. We have previously showed that the suppression of Spry2 effectively induces the periodontal ligament migration along the root surface of the tooth and an increase of the alveolar bone, whereas impeding gingival epithelial down-growth toward bone defects.

Results: In the recent paper in our laboratory, we showed that Spry2 knockdown by Pg lipopolysaccharide (LPS) and interferon (IFN) γ stimulation converts macrophages from the M1 to M2 phenotype, and may effectively resolve inflammation by releasing anti-inflammatory cytokines in macrophages.

Conclusion: These studies show that the topical application of Spry2 inhibitors to bone loss may generate an appropriate environment for periodontal remodeling by inducing M2 macrophages, resolving inflammation in periodontitis, activating the periodontal ligament migration along the root surface of a tooth, promoting growth of the alveolar bone, and interfering with gingival epithelial down-growth toward bone defects. These findings thus provide a molecular basis for novel therapeutic targets in periodontal remodeling.

Sprouty2 suppression showed decreased activation of ERK, thereby inducing gingival epithelial cell proliferation [20]. Furthermore, we found showed that Spry2 depletion promoted cell migration and proliferation, whereas it interfered with differentiation to osteoblasts in periodontal ligament stem cell line [21]. Thus, Spry2 knockdown may effectively induce migration of the periodontal ligament along the root surface of a tooth, and the increase of alveolar bone, while impeding the down-growth of gingival epithelia in bone defects. These two previous studies indicated that Spry2 deletion may create favorable conditions in periodontal regeneration. The inflammation caused by Pg LPS must be resolved, and M2 alternative activated macrophages play an important role in periodontal wound healing during the start of periodontal remodeling. Accordingly, it is fundamental to examine the physiological mechanisms through which the downregulation of Spry2 by the stimulation with Pg LPS influences macrophage functions.

In the recent paper in our laboratory entitled “Inhibition of Sprouty2 polarizes macrophages toward an M2 phenotype by stimulation with...”
interferon γ and Porphyromonas gingivalis lipopolysaccharide”, we found that inhibition of Spry2 in combination with Pg LPS and IFNγ converts macrophages to the M2 phenotype, and may effectively resolve inflammation by producing anti-inflammatory cytokines such as IL-10 and various types of growth factors in macrophages [22].

First, Spry2 knockdown promoted the activation of growth factor-induced AKT/phosphoinositide 3-kinase (PI3K) and Rho family GTPases, specifically Rac1, in macrophages, thereby increasing the efferocytosis of apoptotic cells after Pg LPS and IFNγ stimulation. In addition, we demonstrated that the recognition and engulfment of apoptotic cells, called “efferocytosis”, result in the release of anti-inflammatory cytokines, including IL-10 by the suppression of Spry2 [22]. Second, AKT/PI3K signaling can activate TLR pathway induced by LPS in a feedback loop which suppresses the phosphorylation of TLR activators. Our experiments suggested that AKT/PI3K suppressed by Spry2 promoted the activation of NFκB p65 and IκB degradation.

Figure 1: Function of the Spry2 inhibitor in the growth-factor signaling pathway in various types of cells. The suppression of Spry2 inhibits endogenous Spry2, thereby activating growth factor-induced Rac1 pathway and inhibiting the TLR-induced NFκB pathway in macrophages. In addition, it induces phenotypic changes toward the M2 type in macrophages, enhancing bFGF and EGF. These factors are involved in the anti-inflammatory functions of osteoblasts, gingival epithelial cells, and periodontal ligament cells, leading to periodontal tissue remodeling.

Figure 2: A proposed image of the clinical administration of Spry2 inhibitors. The topical administration of Spry2 inhibitors can be utilized to resolve inflammation effectively in periodontal tissue. M2 macrophages (gray) polarized by Spry2 inhibition may generate an appropriate environment for periodontal remodeling by activating the periodontal ligament migration along the root surface of a tooth (green), promoting growth of the alveolar bone (blue), and interfering with the down-growth of gingival epithelia toward bone loss (purple).
These interactions between TLR and RTK pathway such as growth factor signaling decreased interference with polarization toward M1 macrophages [22]. Consequently, our results demonstrate that Spry2 inhibitors suppress endogenous Spry2, thereby inducing the activation of growth factor-induced Rac1 and AKT/PDK3, and inhibiting the TLR-induced NFκB pathway in macrophages. Moreover, Spry2 suppression induces change of the macrophage phenotype toward the M2 type, and enhances the production of bFGF and EGF, which are involved in the cell functions between osteoblasts, gingival epithelial cells, and periodontal ligament cells (Figure 1). Taken together, these studies show that the topical application of Spry2 inhibitors to bone loss may generate an appropriate environment for periodontal remodeling by inducing M2 macrophages, resolving inflammation in periodontitis, activating the periodontal ligament migration along the root surface of a tooth, promoting growth of the alveolar bone, and interfering with gingival epithelial down-growth toward bone defects (Figure 2). These findings thus provide a molecular basis for novel therapeutic approaches in periodontal tissue regeneration.

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Author Disclosure Statement

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