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Editorial
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How Sphingosine-1-Phosphate and Its Receptor Signaling Affect Periodontitis?

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Editorial

Sphingosine-1-Phosphate (S1P) is a bioactive sphingolipid, which can be generated by various stimuli including bacterial lipopolysaccharide (LPS) and cytokines [1,2]. S1P binds to five G protein-coupled receptors (S1PR1-5) on the plasma membrane, which regulate an array of signaling pathways and play essential roles in the pathogenesis of many diseases including cancer, atherosclerosis, rheumatoid arthritis, diabetes, and osteoporosis [3-5]. However, how S1P and its receptor signaling affect periodontitis have not been elucidated. Constitutive levels of S1P in most tissues are very low (10 nM to 30 nM), because S1P is either degraded by S1P lyase or dephosphorylated by S1P phosphatase in tissues (Figure 1). In contrast, S1P levels in the blood are very high (150 nM to 1,000 nM), because erythrocytes and platelets generate abundant S1P, but erythrocytes and platelets lack both S1P lyase and S1P phosphatase [2,6]. Therefore, there is a sharp S1P gradient between the blood and tissues, which controls the migration of monocytes from blood to tissues [7,8].

Our previous study [9,10] demonstrated that the oral pathogen *Aggregatibacter actinomycetemcomitans* (*Aa*) induced the generation of S1P in macrophages. Moreover, we demonstrated that S1P is a chemoattractant, which dose-dependently induced the chemotaxis of bone marrow-derived monocytes and macrophages (BMMs, osteoclast precursors) [10]. Elevated levels of S1P affect bone resorption in postmenopausal women [11], rheumatoid arthritis induced by TNF-α [12], as well as oral pathogen *Aa*-induced alveolar bone loss. During periodontitis, oral bacterial pathogens stimulate the generation of proinflammatory cytokines and S1P, which attract monocytes from blood circulation to periodontal tissues. These monocytes can further differentiate and fuse to form multinucleated osteoclasts, leading to alveolar bone loss and tooth loss. Future studies need to determine how S1P receptor signaling affect the chemotaxis of monocytes induced by bacterial infection.

Oral pathogens stimulate the generation of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and receptor activator of nuclear factor kappa-B ligand (RANKL). These proinflammatory mediators promote osteoclastogenesis and subsequent alveolar bone loss. Our recent study [13] demonstrated that S1P receptor 2 (S1PR2), couples with Gi, Gq, and $G_{12/13}$ family proteins, plays a key role in modulating the proinflammatory cytokine response induced by the oral pathogen *Aa* and S1PR2 regulates osteoclastogenesis induced by RANKL. Knockdown of S1PR2 by a specific S1PR2 shRNA significantly reduced IL-1β, IL-6, and TNF-α protein levels induced by *Aa* compared with controls. Moreover, knockdown of S1PR2 by the S1PR2 shRNA inhibited osteoclastogenesis and suppressed bone resorption induced either by RANKL alone or co-stimulated by RANKL and *Aa*-stimulated cell culture media compared with controls [13]. Mechanistically, we demonstrated that S1PR2 shRNA significantly suppressed osteoclastogenic factors, including the nuclear factor of activated T-cells cytoplasmic calcineurin-dependent 1 (NFATc1), cathepsin K (Ctsk), acid phosphatase 5 (Acp5), osteoclast-associated receptor (Oscar), dendritic cells specific transmembrane protein (Dcstamp), and osteoclast stimulatory transmembrane protein (Ocstamp) induced by RANKL in bone marrow cells compared with controls [13]. Our studies suggest that suppressing S1PR2 might be a novel therapeutic strategy to treat periodontitis.

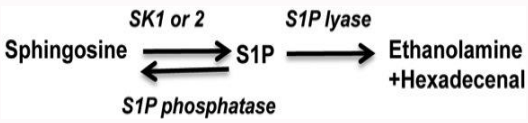

Figure 1: S1P biosynthesis and degradation. S1P can be generated from sphingosine by sphingosine kinase (SK) 1 and /or 2. S1P can be degraded by S1P lyase or dephosphorylated by S1P.

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