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

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Editorial

Sphingosine-1-Phosphate (SIP) is a bioactive sphingolipid, which can be generated by various stimuli including bacterial lipopolysaccharide (LPS) and cytokines [1,2]. SIP binds to five G protein-coupled receptors (SIPR1-5) 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 SIP and its receptor signaling affect periodontitis have not been elucidated. Constitutive levels of SIP in most tissues are very low (10 nM to 30 nM), because SIP is either degraded by SIP lyase or dephosphorylated by SIP phosphatase in tissues (Figure 1). In contrast, SIP levels in the blood are very high (150 nM to 1,000 nM), because erythrocytes and platelets generate abundant SIP, but erythrocytes and platelets lack both SIP lyase and SIP phosphatase [2,6]. Therefore, there is a sharp SIP 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 SIP in macrophages. Moreover, we demonstrated that SIP is a chemoattractant, which dose-dependently induced the chemotaxis of bone marrow-derived monocytes and macrophages (BMMs, osteoclast precursors) [10]. Elevated levels of SIP 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 SIP, 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 SIP 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 SIP receptor 2 (SIPR2), couples with Gi, Gq, and G12/13 family proteins, plays a key role in modulating the proinflammatory cytokine response induced by the oral pathogen Aa and SIPR2 regulates osteoclastogenesis induced by RANKL. Knockdown of SIPR2 by a specific SIPR2 shRNA significantly reduced IL-1β, IL-6, and TNF-α protein levels induced by Aa compared with controls. Moreover, knockdown of SIPR2 by the SIPR2 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 SIPR2 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 SIPR2 might be a novel therapeutic strategy to treat periodontitis.

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

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