THE ROLE OF PROSTAGLANDIN (PGE2) IN ALVEOLAR BONE DESTRUCTION

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Abstract

Inflammation chronic diseases in gingiva and periodontium tissue cause destruction of alveolar bone. Periodontopathy bacteria cause periodontal tissue destruction by host cell activating system, such as prostaglandin. PGE_2 induce bone resorption and MMP secretion (Academic report, 1999). Prostaglandin E_2 (PGE_2) is formed as a result of the metabolism of arachidonic acid. It participates in inflammatory response. Prostaglandin cause alveolar bone destruction by osteoclast activating. Beside it, it enhance calcium metabolism.

Keywords: prostaglandin, alveolar bone destruction, osteoclast

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Inflammation chronic diseases in gingiva and periodontium tissue cause destruction of gingiva connective tissue, periodontal ligament, and alveolar bone. Clinically, the inflammation is seen redness, swelling, and bleeding on probing. In cellular and molecular, inflammation process is showed by cellular infiltration and releasing some of cytokine. The main provoking factor induce gingiva tissue inflammation is biofilm bacteria (dental plaque) on teeth surface or gingiva interfaces.[1] Periodontopathy bacteria cause periodontal tissue destruction by host cell activating and system to produce and release enzyme and the other molecule. These can destroy periodontal tissue and this activity will be regulated by inflammation mediator.[2]

The bacteria will invade in periodontal tissue and release soluble bacterial factor. One of soluble bacterial factor is lipopolysacharide (LPS). LPS is play role in pathogenesis of alveolar bone destruction. LPS is potent material for stimulating bone resorption in vitro and in vivo. LPS induce production of osteoclast in bone marrow culture or injected in femur bone. It is showed by number of osteoclast in increasing and infiltration on bone surface. LPS also induce some locally factor production, such as Tumor Necrosis Factor - a (TNF-a), interleukin 1 (IL-1), and prostaglandin E_2 (PGE_2) from macrophage, fibroblast, and osteoblast cell in inflammation periodontal tissue.[3] The aim of this study is to know the role prostaglandin (PGE2) in alveolar bone destruction.

PROSTAGLANDIN E_2 (PGE_2)

PGE2 is eicosanoid vasoactive that produced by monocyte and fibroblast. Eicosanoid signal transduction pathways are highly conserved across vertebrate species. The prostaglandins, a subset of the eicosanoid family of signaling molecules, are involved in a number of physiological processes in many tissues. Functions of Prostaglandins are a variety of physiological effects including:

1. Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.
2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.
3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor.
4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.

Prostaglandins are synthesized from arachidonic acid (AA) first by cyclooxygenase (Cox)1 or 2, which convert AA into PGH2. This precursor PG is further processed by isoform specific cytosolic or microsomal prostaglandin synthases (c/mPGES) to become PGE2 or one of several other effector prostaglandins. The roles of Cox1 and Cox2 in prostaglandin production do not wholly overlap; Cox1 appears to be responsible for the majority of constitutive signaling, while Cox2 acts in an inducible fashion. It has been suggested that Cox1 and cPGES, and Cox2 and mPGES, respectively, work in cooperation. This model may oversimplify the role of the two prostaglandin syntheses, as increasing evidence implies that the requirement of each enzyme for PG production is specific to

both cell type and function. PGE2 signals in either an autocrine or paracrine manner through four specific G protein coupled E prostanoid (EP) receptors. Positive signal transduction receptors include EP1, which triggers mobilization of intracellular Ca2+, and EP2 and EP4, which both stimulate cyclic AMP (cAMP) production. EP3 acts as a negative effector to inhibit cAMP. There is evidence to indicate that EP2 and EP4 are affected differently by PGE2; EP4 quickly becomes desensitized to PGE2 and cannot bind its metabolites, while EP2 displays no such desensitization and is able to bind several PGE2 metabolites with varying affinities. This would imply that PGE2 signaling is regulated distinctly on the levels of Cox, PGES, and EP receptors though no conclusive results have yet been produced to support this model.[4]

PGE_2 induce bone resorption and MMP secretion.[5] Prostaglandin E_2 (PGE_2) is formed as a result of the metabolism of arachidonic acid. It participates in inflammatory response. Pro inflammatory effect of PGE_2 are increasing vasodilatation, enhancing responsiveness of receptors to painful stimuli, releasing of collagenase by inflammatory cells and activation of osteoclast thereby causing bone resorption.[6] PGE2 is a derivative of arachidonic acid that induces periosteal and endocortical bone formation, principally by stimulating local osteoprogenitor cells on the adjacent endocortical surface. The anabolic effect of PGE2 demonstrated in long bones may also occur in the mandible. Particularly as local delivery of prostaglandin E1 (PGE1) has been shown to enhance the formation of mandibular alveolar bone, reorganization of adjacent cells in the periodontal ligament and cementum formation. The positive effect of PGE2 on bone deposition has been reported with doses as low as 1 mg/kg per day delivered subcutaneously into different animal models over extended periods of time.[7]

ALVEOLAR BONE RESORPTION

Bone is a dynamic multifunctional organ that is comprised of a structural framework of calcified matrix containing populations of many cell types including chondrocytes, osteoblasts, osteocytes, osteoclasts, endothelial cells, monocytes, macrophages, lymphocytes, and hematopoeitic cells. Bone tissue is constantly being remodeled throughout life in response to hormonal signals, paracrine and autocrine factors, and physical stresses.[8]

Alveolar bone is remineralized connective tissue. It is part of maxillary and mandible that support teeth. Alveolar bone is consist anorganic matrix (67 %) and organic (33 %). Organic matrix is consist 28 % collagen and 5 % non collagen.[9] Alveolar bone can be destruction by overloading of mastication and plaque bacteria activity in periodontal diseases. Plaque bacteria cause differentiation of bone progenitor cell to be osteoclast and stimulate gingival cell to release inflammation mediators.[10] The role of osteoclasts in causing bone loss involved pro-inflammatory cytokines such as IL-1 (interleukin -1), IL-6, TNF-β (tumor necrosis factor – β), GM-CSF, and prostaglandin E2. These cytokines and prostaglandins were found to increase osteoclast proliferation.

Bone resorption is complex process that related by bone surface loss (*lacuna howship*) and increasing of number of multinuclear cell (osteoclast) morphologically. Osteoclast is from hemopoetic system, monocyte and macrophage. Monocyte and macrophage is differenced by cell fusion to multinuclear cell. It is stimulated by local and systemic factor. When osteclast is active, osteoclast produces hydrolytic enzyme. This enzyme will digested bone organic materials.[3]

Alveolar bone resorption in periodontal disease is related by bacteria and host interaction. Bacteria plaque products induce progenitor bone cells differentiation to be osteoclast and induce gingiva cells to release inflammatory mediator. Inflammatory mediator also influences progenitor bone cells differentiation. Plaque product and inflammatory mediator can inhibit activity and number of osteoblast or progenitor cell directly. Host cells also release some factors that can induce bone resorption, such as prostaglandin and its precursors, IL 1-a, IL 1-β, and TNF-a.[11]

The remodeling process involves four following steps: activation, resorbtion, reversal, and formation.[8]

1. Activation. The initiation of osteoclastic bone resorption depends on the interaction between cells of the osteoblastic and hematopoietic system. Fibroblasts secrete collagenase and other matrix-destroying enzymes, leading to altered tissue integrity. Fibroblast growth factor-23 (FGF23) was first discovered as an important factor for mineral homeostasis. Osteoblastic cells can activate hematopoietic cells to differentiate into bone resorbing osteoclasts through the production of macrophage colony stimulating factor (M-CSF) and receptor activator of NFB ligand (RANKL). Lining cells of osteoblastic origin on the bone surface may also play a role by secreting proteolytic enzymes that remove a protein layer which normally covers the mineralized matrix.
2. Resorption. Osteoclasts bind to the mineralized matrix through vitronectin receptors and then form their resorbing apparatus consisting of a ruffled border. Resorbing apparatus will secrete hydrogen ions and matrix degrading enzymes, particularly Cathepsin K. This permits the establishment of a low pH and a high concentration of enzymes

that can degrade collagen quite effectively at that low pH. In addition to this cellular compartmentalization there may be a compartmentalization of the entire bone remodeling unit because the lining cells remain intact above the osteoclastic resorption and osteoblastic formation sites. This might allow for growth factors released from osteoclasts or matrix during resorption to remain for longer and at more effective concentrations during the next phase.

3. Reversal. After osteoclastic resorption is complete there is a reversal phase during which mononuclear cells, which may be either of the mesenchymal or hematopoietic lineages, complete the removal of matrix and prepare the bone for formation by laying down a "cement line" of non-collagen proteins.
4. Formation. In the formation phase osteoblasts lay down matrix, which becomes gradually mineralized. As each layer of osteoblasts forms its assigned amount of matrix it either undergoes apoptosis, or becomes buried in the matrix as an osteocyte. As this process of replacing the resorption cavity is completed, some of the osteoblasts may remain on the surface as lining cells.

THE ROLE OF PROSTAGLANDIN (PGE2) IN ALVEOLAR BONE DESTRUCTION

Oral bacteria in dental plaque invade in periodontal tissue. It will release soluble bacteria factor, such as lipopolysacharide (LPS), and penetrate to sulcular epithelium.[12] LPS induce inflammation in periodontal tissue by activating host response (macrophage, fibroblast, and osteoblast) to produce pro-inflammatory mediator, such as vasoactive amine (histamine and serotonin), arachidonic acids (prostaglandin and leukotrin), and cytokine (tumor necrosis factor and interleukin). [2]

These product recruit neutrophils to the area and influence chemotaxis. Vasoactive and prostaglandin cause the vessels to dilate or increasing of permeability of gingiva vessel. It causes passage of virtually all of the component of the blood into the connective tissue, such as pro-inflammatory mediator, complement, plasma protease, plasmin and kinin. Pro-inflammatory mediator will influence physiology system, especially prostaglandin.[2,3,13]

Cox 1 is expressed in normal bone, while cox 2 expressions are up regulated during bone repair and under pathological condition such as inflammation and neoplasia. Thus, the skeleton is abundantly supplied with prostaglandins, especially PGE2. Prostaglandin are synthesized and secreted by localized host cell response have been shown to stimulate osteoclastic bone resorption. PGE play a stimulatory or an inhibitory role in bone metabolism, depend on the physiological or pathological circumstances. PGE2 mediated resorption contributes significantly to bone loss related inflammation diseases and in response to prolonged immobilization.[14]

Prostaglandin E_1, E_2 and F_2 (PGF_2) are potent stimulators of bone resorption. Some studies show PGE_2 will increase alveolar bone resorption and the effective dose is 10^{-8}M. If the dose is more than 10^{-8}M, alveolar bone resorption or decalsification will not increase.[15,16,17]

The anabolic effect of prostaglandin on bone has been demonstrated by systemic administration on PGE2, which stimulates bone formation and increases bone mass in infant and animals. Under specific pathological condition, prostaglandin, especially PGE2 can stimulate bone resorption by increasing the amount and functional activity of osteoclast.[14]

The action prostaglandin induces alveolar bone resorption by activating osteoclast activity to release calcium ion on bone surface in both in vivo and in vitro. It has been shown that hormones and cytokines involved in bone resorption can stimulate cox 2 and prostaglandin synthesis. Experimental animal carrying genes that have been made inoperative for cox 2 and PG receptors (knockout mice) have impaired osteoclastogenesis and decreased bone resorption. Elevated secretion of inflammatory cytokines and PGE2 is related to the bone loss taking place in some inflammatory disease, including arthritis and periodontitis.[14]

Prostaglandin also causes hyperplasia of osteoclast population, activation of pre-existing osteoclast and increasing of osteoclast size. When PGE_2 administer for the first time, PGE_2 will stimulate maturation of pre-osteoclast like mononuclear cells in the perivascular region on the periodontium to stimulate fusion of the mononuclear cells. Prostaglandin might influence proliferation and differentiation osteoclast progenitor cells and osteoclast like cells to be osteoclast. All of them make production of osteoclast increase. They will stimulate activity and increase number of osteoclast, so releasing of calcium ion will increase. Finally, it causes alveolar bone resorption.[18]

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