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REVIEW **Open Access**

Profiles of inflammation factors and inflammatory pathways around the peri-miniscrew implant

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Summary. Background. Peri-miniscrew implant is a temporary assistant armamentarium for the treatment of severe malocclusion and complex tooth movement, the inflammation around it is the main reason for the failure of orthodontic treatment due to the implant loosening and falling out. Inflammation around the peri-miniscrew implant is associated with the release of pro-inflammatory cytokines. These pro-inflammatory cytokines, in turn, recruit immune cells (such as macrophages, dendritic cells, T cells, and B cells), which can produce and release inflammatory biomarkers, regulate the interaction between immune cells, periodontal ligament cells, osteoblasts, and so on. However, there is currently no effective clinical treatment plan to prevent inflammation around implants.

Purpose. To investigate the potentially essential factors in the inflammatory response around the peri-miniscrew implant and explore the signaling pathways involved.

Methods. Here, we review the studies focused on inflammatory biomarkers (Interleukins, tumor necrosis factor-α (TNF-α), receptor activator of NF-ϰB ligand (RANKL), matrix metalloproteinases (MMPs), and cellular adhesion molecules (CAMs)) in peri-miniscrew implant crevicular fluid (PMICF), as well as inflammatory signaling pathways (Wnt5a, JNK, Erk1/2, NF-ϰBp65 and TAB/TAK) in periodontal cells from 1998 to 2020.

Results. A literature search revealed TLR-2, TLR-4, LOX-1, and BMPs are involved in regulating ILs (IL-1β, IL-6, IL-8, and IL-17), TNF-α, RANKL, MMP-2, MMP-9 expression via JNK, Erk1/2, Wnt5a, NF-ϰBp65, OPN, and TAB/TAK signaling pathways. Among them, IL-1β and IL-6 are the critical inflammation factors in the signaling pathways inducing the inflammatory reaction surrounding implants. Besides, CAM-1 was also regulated by MMP-9 and IL-17.

Conclusion. There are considerable potential factors involving regulating inflammatory biomarkers on downstream signaling pathways in peri-minisrew implant crevicular fluid.

Clinical significance. This review provides the substantiation of these cell factors and signaling pathways around peri-miniscrew implants, proposes more practical clinical therapeutic ideas and schemes for improving the stability and clinical efficacy of peri-miniscrew implants.

Key words: Inflammation, Cytokines, Peri-miniscrew implant

Introduction

The manifestation and achievement of orthodontia with balanced, stable, and aesthetically pleasing orthodontic results requires correct diagnosis, well-designed treatment plans, and accurate anchorage control. Anchorage here refers to structures that can

Abbreviations. peri-miniscrew implant crevicular fluid, PMICF; tumor necrosis factor-α, TNF-α; receptor activator of kappa-B nuclear factor kappa-B, RANK; receptor activator of NF-kB ligand, RANKL; matrix metalloproteinases, MMPs; cellular adhesion molecules, CAMs; low-level laser therapy LLLT; gingival crevicular fluid, GCF; interleukins ILs; lectin-type oxidized LDL receptor 1, LOX-1; peri-implant crevice fluid PICF; c-Jun N-terminal kinase, JNK; Toll-like receptor 2 TLR-2; Osteopontin, OPN; recombinant human bone morphogenetic protein-2, rhBMP-2; TAK1 binding protein/transforming growth factor β-activating kinase 1, TAB/TAK; fluorohydroxyapatite, FHA; osteoclast inhibitory factors, OCIF; extracellular matrix, ECM; TNF receptor-associated factor 6, TRAF6; soluble intercellular adhesion molecule 1, sICAM-1

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resist the counterforces to orthodontic forces, and it is difficult for traditional anchorage to provide stable and effective absolute anchorage independent of patient cooperation. The emergence and clinical use of miniscrew implants provide a new choice for orthodontic anchorage control, and it is a practical auxiliary appliance for the treatment of severe malocclusion and complex tooth movements, which relieves the dependence of the anchorage results on patient cooperation. Miniscrew implants are widely used in clinical settings due to their tiny size, simple implantation process, minimal trauma, flexibility concerning the site of implantation, and good patient tolerance.

Poor oral hygiene and inflammation of peri-implant tissues have been the leading causes of failure in miniscrew implant implantation. Peri-miniscrew implant inflammation is referred to as chronic progressive marginal inflammation occurring in peri-miniscrew implant tissues. The main symptoms of peri-miniscrew implant inflammation are progressive loss or progressive destruction of supporting peri-miniscrew implant tissues, including soft tissues and bone tissues (Jepsen et al., 2015; Ramanauskaite and Juodzbalys, 2016). The main clinical manifestations are hyperemia and hemorrhage of soft tissue around the peri-miniscrew implant, the proliferation of soft tissue around the minimally invasive implant, loosening and falling out of the minimally invasive implant because of the destruction of surrounding tissue due to inflammation (Park et al., 2006).

Sometimes, the peri-miniscrew implant inflammation has been associated with a gram-negative anaerobic microbiota infection, similar to that found in severe periodontitis around natural teeth. Peri-miniscrew implant inflammation encompasses the criteria of peri-mucositis and the addition of loss of osseous support.

Although bacterial insult is identified as the main cause of peri-mucositis, peri-miniscrew is considered to be initiated by stress factors caused by a poor biomechanical environment.

30% peeling off of anchorage nail was caused by peri-miniscrew implant inflammation. After excluding surgical factors and local oral infection, many bone integration and non-severe inflammatory reactions in the later stage of implantation can effectively improve miniscrew implants' stability and promote the effective anchorage control required for orthodontic treatment. To improve hyperemia and hemorrhage of peri-miniscrew implant soft tissues, period line ointment (2% minocycline hydrochloride ointment) is applied at the implantation point. Furthermore, antiseptic mouthwash, teeth brushing (Topouzelis and Tsaousoglou, 2012), and an oral irrigator can maintain oral hygiene by controlling bacteria adhesion. Low-level laser therapy (LLLT; diode laser 660 nm, 40 mW, 1 minute, 2.4 J of total energy) can inhibit inflammation and modulate bone remodeling, thus effectively alleviating patients' discomfort reducing the risk of mini-implant failure (Yanaguizawa et al., 2017). If severe inflammation of peri-miniscrew implant occurs around the small incision, the patient receives analgesics to minimize pain and antibiotics to prevent infection before eventual loosening (Takaki et al., 2010). But severe inflammation of peri-miniscrew implant is still not well controlled in the clinical setting. This paper reviews the abnormal expression of inflammatory biomarkers in peri-miniscrew implant crevicular fluid (PMICF), the specific mechanism of action, and the degree of clinical inflammation infection. It provides a novel idea and schemes for clinical treatment to reduce the rate of anchorage nail shedding caused by peri-miniscrew implant inflammation and effectively control the inflammation infection.

Inflammation factors effect in peri-miniscrew implant

Bone is a tissue that undergoes continuous building and degradation. This tightly regulated remodeling process can be disturbed by many factors. Chronic peri-miniscrew implant inflammation can also perturb alveolar bone metabolism and promote increased bone loss. Enhanced mediators of osteoclastogenesis in resident cells found in the healthy peri-implant compartment and the local synergistic action of cytokines secreted by such cells results in the genesis of resorptive active osteoclasts.

The microcrack hypothesis indicates that microscopic cracks are formed after miniscrew implants due to the elastic difference between the bone and the miniscrew implant (Shank et al., 2012). These microcracks are believed to be repaired by calcium phosphate-induced bone mineralization, but if the concentration of local acidic substances increases, the repair process may be delayed during inflammation or microbial invasion (Bartold et al., 2011). In some reports, miniscrew implants placed 1 mm below the mucogingival junction do not produce serious inflammation. In the process of miniscrew implantation, the local temperature around the implant rises to 47°C for more than 1 min, which may cause cell necrosis at the microcracks and change the biomarkers in PMICF at the interface. PMICF originates from the exudation of plasma and tissue fluid, and it infiltrates the gap between the miniscrew implant and the attached gingiva through periodontal connective tissue (Kapoor et al., 2014). The composition and exudation of the PMICF are affected by the health status and the capillary permeability of the peri-miniscrew implant tissues. The document of the PMICF is similar to that of gingival crevicular fluid (GCF), which contains inflammatory biomarkers such as interleukins (IL-1β, IL-6, IL-8, and IL-17), growth factors, tumor necrosis factor (TNF-α), receptor activator of NF-ϰB ligand (RANKL), matrix metalloproteinases (MMPs) and cellular adhesion molecules (CAMs). These components are similar to those in GCF during orthodontic tooth movement. Studies have shown that the biomarkers in the PMICF during peri-implantitis are identical to those in GCF

during gingivitis and periodontitis. According to previous studies, the presence of inflammation can be confirmed by detecting changes in biomarkers in PMICF, such as interleukins (IL-1β, IL-2, IL-6, and IL-8), growth factors, TNF-α, and RANKL (Kaur et al., 2017). After miniscrew implantation, blood and tissue exudates come into contact with the implant. Subsequently, fibroblasts are induced and reach around the implant, followed by the secretion of collagen extracellular attached to the implant surface. There is a bio-seal layer between the miniscrew implant and the surrounding soft tissues. The loose cell connection helps neutrophils leak into the surrounding soft tissues from the intercellular space during inflammation or infection. The integrity of the sealing area is also affected by the inflammation surrounding the peri-miniscrew implants. Inflammatory exudates through this process increase the clinical infection of the tissue around the miniscrew implants, which results in the implant loosening and then the implant falling out during the stage of providing mobile tooth movement support. Therefore, these inflammatory exudates play an essential role in the excellent adaptation and stability of miniscrew implants.

Relative inflammation biological factors and signaling pathway

Interleukins

Interleukins (ILs) are a group of pro-inflammatory cytokines produced by fibroblasts, osteoclasts, and polymorphonuclear leukocytes. They play a crucial role in the immune response of peri-miniscrew implant inflammation. ILs, such as IL-1β, IL-2, IL-4, IL-6, IL-8, IL-17, and IL-20, can be detected in the PMICF (Table 1). ILs in peri-implant inflammation had been thoroughly investigated. However, few studies have investigated the role of ILs and related signaling pathways after implant anchorage implantation.

IL-1 is a cytokine with a wide range of biological activities. It is mainly produced by lymphocytes and macrophages, is involved in immune regulation, mediates the inflammatory response, produces heat, and causes several pathological lesions. As two independent members of the IL-1 family, IL-1α and IL-1β proteins can recognize receptor IL-1R on the same target cells and produce the same biological effects. IL-1 plays an essential role in the physiological and pathological process of periodontal tissues. Studies have shown that IL-1 can activate lymphocytes, macrophages, and endothelial cells, mediate the release of prostaglandins, and induce inflammatory cell aggregation, fibrinolysis, and bone demineralization by increasing the expression of plasminogen and metalloproteinase genes during periodontal inflammation. All of this makes IL-1 one of the most critical cytokines capable of causing periodontal tissue damage. This leads to falling off of peri-miniscrew implant falling out, and the orthodontic treatment fails. IL-2 is a pro-inflammatory cytokine produced by type 1 T-helper cells. It is involved in bone resorption, which activates osteoclast activity and plays an active role in periodontal diseases' pathogenesis. IL-4 can inhibit the release of pro-inflammatory cytokines.

Moreover, IL-4 can also inhibit the receptor activator of osteoclast formation induced by nuclear factor ϰ-B ligand and inhibit bone resorption, reduce the production of Th1 cells, macrophages, and IFN-γ cells. The anti-inflammatory cytokine IL-4 noticeable changes in rats with experimental periodontitis, but don't support by enough clinical case reports. IL-6 regulates the immune response of inflammatory sites, has autocrine/paracrine activities, and stimulates osteoclast formation and the resorption of bone by osteoclasts. However, current studies have found that it has no significant effect on clinical orthodontic treatment (Berezniakova and Cheremisina, 2017). IL-8 belongs to the CXC-chemokine subclass. IL-8 functions in the assimilation and activation of neutrophil leukocytes and is an essential regulator of neutrophils involved in the occurrence and development of periodontal diseases. IL-8 also promotes lysosomal enzyme activity and phagocytosis. The change of IL-8 concentration in periodontal tissues is an important parameter reflecting periodontal inflammation, and it is one of the markers of alveolar bone resorption. Its role in the occurrence and development of peri-implant inflammation has been reported. Increased levels of IL-8 were observed in the PMICF when more IL-8 was synthesized by the cells around the miniscrew implant.

In a clinical trial conducted in 2007, the results showed no significant differences in IL-1β levels in the peri-microsrew crevicular fluid during the three-week study, which reflected the microscrews used in the study were healthy. There were no statistical differences in the

Table 1. Overview of Interleukins expressed in peri-miniscrew implant.

ILs	Source	Assembly	Location	Expression	Reference
IL-1β	Macrophages	Heterodimer	Plasma memebrane	High	Lo et al., 1999
IL-2	T helper 1 cells	Heterodimer	Endosomal	High	Hamamci et al., 2012
IL-4	T cells	Heterodimer	Endosomal	Unchanged	Cesur et al., 2019
IL-6	Muscle	Heterodimer	Plasma membrane	Unchanged	Hamamci et al., 2012
IL-8	Macrophages	Heterodimer with CXCR1 and CXCR2	Plasma membrane	High	Hamamci et al., 2012
IL-17	T cells	Heterodimer	Endosomal	High	Severino et al., 2011

levels of IL-1β between the control group and implant group, indicating that the mechanical stress of the healthy microscrews may not affect the levels of IL-1β in the peri-microscrew crevicular fluid (Sarı and Uçar, 2007). But the level of IL-1β in PMICF was significantly increased after 1-24h implantation in patients with first bicuspid orthodontic tooth extraction using miniscrew implants as indirect anchorage. It hints that the implanted anchorage and active inflammation occurred (Monga et al., 2014). It was found that the concentrations of IL-1β, IL-6, and IL-8 increased at 8 hours after implantation, which may be due to acute inflammatory reactions caused by implantation surgery, probably due to the inflammatory changes of cells caused by orthodontic mechanical force. The IL-8 level at 24 hours after implantation and 24 hours, 50 days, and 100 days after orthodontic force loading were significantly different from those in the control group, reaching the highest level 24 hours after implantation. Therefore, it is hypothesized that the orthodontic force of orthodontic miniscrew implants can affect the production of peripheral cytokines and that controlling the orthodontic pressure can prevent the accumulation of cytokines and implant shedding (Hamamcı et al., 2012) . Hamamci assessed the concentrations of IL-2, IL-6, and IL-8 in PMICF at 7 time points. These results indicate that the changes of IL-2, IL-6, and IL-8 levels in PMICF of the treatment group and miniscrew implant group are similar, and these values increased in the early stages, indicating that acute stress responses occur. And this may lead to miniscrew implant shedding. To reduce the secretion of local cytokines and avoid loosening the implant, the loading strength of the miniscrew implant should be controlled (Hamamcı et al., 2012). According to the study of the relationship between different miniscrew implant materials and inflammatory responses, only a few ILs, such as IL-1β, IL-2, IL-4, IL-6, and IL-8, were assessed. Various activities of IL-8 indicate that this cytokine plays a significant role in mediating the inflammatory response. Sari et al. suggested that more extended study periods and sampling times are needed to confirm the relationship between IL-1β and the implantation of miniscrews (Sarı and Uçar, 2007). The level of IL-17 increased in the peri-implant crevicular fluid of patients with peri-implant mucositis and peri-implantitis (Severino et al., 2011). Further study is necessary to get fully understand the situation of surrounding peri-miniscrew conditions to enhance their stability.

Regarding the signaling pathway of ILs cytokine in PMICF, the studies showed that the expression of lectin-type oxidized LDL receptor 1 (LOX-1), IL-1β, MMP-2, and MMP-9 increased in the peri-implant crevice fluid (PICF) of patients with peri-implant inflammation, and LOX-1 induced the production of IL-1β by activating the c-Jun N-terminal kinase (JNK) pathway, thereby promoting the activity of MMP-2 and MMP-9 (Che et al., 2017). Toll-like receptor 2 (TLR-2) signaling and its downstream pro-inflammatory cytokines are believed to play an essential role in developing peri-implant inflammation. The expression of IL-6 and TLR-2 increased, and NF-kB and JNK were involved in regulating TLR-2 on IL-6 in implant inflammation (Li et al., 2019). Osteopontin (OPN) is a phosphorylated glycoprotein secreted by immunocompetent cells, which is involved in the differentiation of odontoblast-like cells and the secretion of type I collagen in the process of pulp healing after tooth transplantation. The OPN expression of THP-1 macrophages stimulated by *Porphyromonas gingivalis* increased in most patients around implants. After pretreatment with LOX-1 inhibitor or THP-1 macrophage inhibitor, the expression of OPN decreased in *Porphyromonas gingivalis*. Gingivitis induces OPN expression through the ERK1/2-MAPK dependent pathway. But OPN is able to decrease the expression of IL-1β in *P. gingivalis* infection (Che et al., 2018). Wnt5a is an activated ligand of the atypical Wnt signaling pathway involved in leukocyte infiltration and cytokine/chemokine production in inflammatory diseases. Previous studies have shown that Wnt5a is significantly upregulated in gingival tissue, chronic aggressive periodontitis, and the gingival tissue of patients around the implant. The production of Wnt5a depends on LOX-1 and TLR-4 levels. Wnt5a gene knockout reduced the production of IL-1β and MMP-2 induced by *p. gingival* infection (Zhang et al., 2020). It was found that the expression of NF - kBp65 and TLR-4 was up-regulated in the periodontal tissues of canine implants, which led to the increase of IL-6, IL-8, and TNF-α expression levels (He et al., 2018). Microstructural implant surface can increase the differentiation of osteoblasts *in vitro* and can be combined with recombinant human bone morphogenetic protein-2 (rhBMP-2) to promote the formation of bone around the implant. It showed that rhBMP-2 might increase IL-6, IL-8, IL-17 through TAK1 binding protein/transforming growth factor β-activating kinase 1 (TAB/TAK) signaling pathway (Hyzy et al., 2013).

Tumor Necrosis Factor-α (TNF-α)

TNF-α is the central factor of inflammation. It is produced by monocytes, macrophages, and osteoblasts, stimulating fibroblasts to produce collagenase and plays an essential role in the inflammatory response of periodontitis and peri-implant inflammation. A study showed that TNF-α was always expressed in the PMICF whether the peri-micro implant tissues around the implant were healthy or inflamed, and the expression of TNF-α in patients with inflammation around the implant was more than that in patients without inflammation. The expression of TNF-α in the peri-micro implant inflammation group was higher than that in the healthy group at each time point. The current results suggested that inflammation might be the initiator for increased TNF-α (Cesur et al., 2019).

TNF-α has dual effects: a chronic high level of TNF-α can inhibit the proliferation and differentiation of

osteoblasts, while a short-term low level of TNF-α can enhance the proliferation and differentiation of osteoblasts. Fini et al. determined the TNF-α content in the artificial PMICF of titanium of fluorohydroxyapatite (FHA) alloy and titanium alloy orthodontic microimplants using ELISA assay (Fini et al., 2003). The results indicated that the gradual release of fluorine in the FHA coating could not only inhibit the growth of peri-implant inflammatory pathogens and reduce the immune response but also do no harm to the human body. The duration of high levels of TNF-α in the FHA group was shorter than in the titanium alloy group, suggesting the higher tissue compatibility and faster osseointegration of the titanium of FHA alloy microimplants. When peri-implant inflammation was induced, the level of TNF-α in both groups increased rapidly over a short duration. However, after removing the inducement, the FHA group's TNF-α content decreased rapidly to a relatively lower level. Therefore, we speculate that FHA does inhibit the occurrence and development of peri-implant inflammation and speed up the recovery from inflammation and osseointegration reconstruction around the micro-implants. This is the application of TNF-α level in materials of peri-implant chosen.

In clinical trials, Kaya found that TNF-α began to increase after 1 hour after tooth movement under loading and lasted for seven days, but the difference was not significant; there was no significant difference between the miniscrew implant group, experimental group, and control group. From day 21 onward, the TNF-α in the PMICF and GCF of each group began to decrease to the baseline level gradually. The increase of TNF-α at the beginning was an acute response to the distal movement of canine teeth. The decrease of TNF-α after seven days may be due to the adaptation of periodontal tissues to the orthodontic force stimulation and the negative feedback mechanism to prevent excessive accumulation of inflammatory mediators, resulting in harmful consequences. Therefore, the TNF-α level is associated with orthodontic force in clinical treatment. Regarding the signaling pathway of TNF-α in PMICF, the results showed that the expression of NF - kBp65 and TLR-4 regulated the expression of TNF-α in the periodontal tissues of canine implants (He et al., 2018).

Receptor activator of nuclear factor Kappa-B ligand

The receptor activator of kappa-B (RANK) is a crucial factor affecting the balance between osteoblasts and osteoclasts. It directly induces osteoclast differentiation and maturation, increases cell activity and promotes bone resorption after binding to the receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL is a member of the TNF cytokine family. It is located on the cell membrane of osteoblasts and interstitial cells, and it is the ligand of OPG/osteoclast inhibitory factors (OCIF), which induce osteoclast differentiation and activate bone resorption. OPG is also the decoy receptor of RANKL produced by osteoblasts, leading to osteoclast apoptosis. The biological effects of OPG on osteoblasts include inhibition of the terminal stage of osteoclast differentiation, inhibition of the activated stromal osteoclasts, and induction of apoptosis (Li et al., 2019).

Bone cells are distributed in the mineralized extracellular matrix (ECM), which plays a critical role in bone formation and remodeling. Osteocyte-driven control of bone formation is achieved by SOST/sclerostin mechanism, while osteocyte-driven control of bone remodeling is performed by a signal mechanism involving RANKL, RANK, and OPG. Studies have shown that activated T lymphocytes lead to high expression of RANKL mRNA in periodontal inflammatory tissues, while OPG mRNA level decreases correspondingly (Enhos et al., 2013). When binding of RANKL to RANK, the adaptor molecule TNF receptor-associated factor 6 (TRAF6) is recruited into the intracellular domain of RANK to induce the activation of nuclear factor kappa B (NF-ϰB) and mitogen-activated kinases, including p38 and Jun N-terminal kinase (Li et al., 2019).

Due to the interactions of RANK, RANKL, and OPG in the functional mechanism of osteoclasts, the RANK/RANKL/OPG ratio determines the occurrence of osteoclasts, and bone remodeling is regulated by RANK-RANKL binding and OPG production. In clinical trials, Enhos et al. assessed the contents of OPG and RANKL in PMICF of two groups. They found that the levels of OPG and RANKL in the load miniscrew implant group were significantly higher than those in the load-free miniscrew implant group on day 4 ($P < 0.05$), while the total OPG in the loaded miniscrew implant group had not significantly increased. In the loaded miniscrew implant group, the concentrations of RANKL and OPG decreased during the first 48 hours after loading, and the amount of PMICF increased 48 hours after loading. They suggested that PMICF is an inflammatory exudate, and the concentrations of OPG and RANKL decreased at 48 hours after loading due to the increase of PMICF. The increase of the OPG/RANKL ratio in the unloaded group may be related to the acute response of the body to the miniscrew implant and bone remodeling. The overall stable OPG/RANKL ratio also reflected that the patients are in good health, and the micro-implants are in good condition (Enhos et al., 2013). Regarding the signaling pathway of RANKL in PMICF, it showed that the level of RANKL protein in the crevicular fluid around implants increased and was regulated by TLR-2, LOX-1, and Erk1/2 signal transduction (Meng et al., 2020).

Matrix metalloproteinase

Matrix metalloproteinases (MMPs) include a large family of zinc- and calcium-dependent extracellular matrix-degrading endopeptidases, which can be categorized into collagenases (MMP-1, -8, and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10,

and -12), matrilysin (MMP-7), and membrane-type matrix metalloproteinases (MT-MMP-1 through -5) (Enhos et al., 2013). MMP-9 is a gelatinase with potential enzymatic activity on denatured collagen (gelatin), native type IV and V collagens, and elastin. Collagen IV and laminin are common components of the basement membrane. The functional domains of MMP-9 include signal peptide domain, N-terminal leading peptide domain, a catalytic domain, zinc ion binding site, fibrin-like structure domain, and original structure domain of V-type glue. The main function of the peptide region is to maintain the stability of the enzyme, in which cysteine sulfhydryl covers the binding site of zinc ions, making MMP-9 inactive. When the region is cut-off by specific enzymes such as MMP-3, pancreatic enzymes, and fibrinolytic enzymes, the active center's zinc-binding site is exposed, and MMP-9 is activated. MMP-9 primarily degrades the components of the extracellular matrix membrane and has a corresponding biological function. MMP-9 can also cleave various non-ECM molecules, such as IL-1β, substance P, myelin basic protein, and amyloid β peptide.

The level of MMP-9 increases in inflammatory tissue. Monocytes/macrophages infiltrate into the areas of chronic inflammation in inflammatory conditions like obesity, arthritis, atherosclerosis, and periodontal disease, in which connective tissue degraded by MMP-9 is thought to trigger disease pathology (Zhou et al., 2012). Studies have shown that cytokine release induced by the inflammatory reaction is a necessary step for the induction of MMP-9 (Gan et al., 2001; Hwang et al., 2009). Cytokines such as TNF-α, IL-1β, and IL-6 can active MMP-9 (for example, 1 μg/L TNF-α or IL-1β can increase the gene expression of MMP-9 and significantly induce the production of MMP-9). Kusano et al. suggested that IL-1 and IL-6 also similarly induce osteoclast formation, which leads to the increase of MMP-9 mRNA expression and the production of MMP-9 protein (Kusano et al., 1998). Under the stimulation of TNF-α, IL-1β, IL-6, and other inflammatory factors, MMP-9 is activated to degrade various extracellular matrices, which plays a vital role in the occurrence and development of periodontitis and peri-implant inflammation. By comparing the MMP-9 concentrations in the PMICF of clinical orthodontic patients with healthy or inflammatory peri-implant, Zeng suggested that the reason may be that almost all cells in periodontal tissues can express one or more metalloproteinases, which increase significantly under the stimulation of inflammatory factors. Combined with the positive correlation between MMP-9 level in PMICF and the results of clinical examination, such as dental plaque score, periodontal bleeding index, and periodontal probing depth, the authors believe that the detection of MMP-9 can indicate the health status of the peri-miniscrew implant tissues and provide an essential basis for early diagnosis of peri-miniscrew implant inflammation. With regard to the signaling pathway of MMPs in PMICF, suggested that LOX-1 activated the JNK pathway and then promoted the activities of MMP-2 and MMP-9 (Che et al., 2017). Besides, LOX-1 and TLR-4 might stimulate the Wnt5a activity to up-regulate the expression of MMP-2 (Zhang et al., 2020).

Cellular adhesion molecule

Cellular adhesion molecules are involved in the interactions between cells and the extracellular matrix. Cellular adhesion refers to the adhesion between cells, which allows the exchange of information between cells. The soluble transmitters for information exchange are called cellular adhesion molecules (CAMs). Soluble

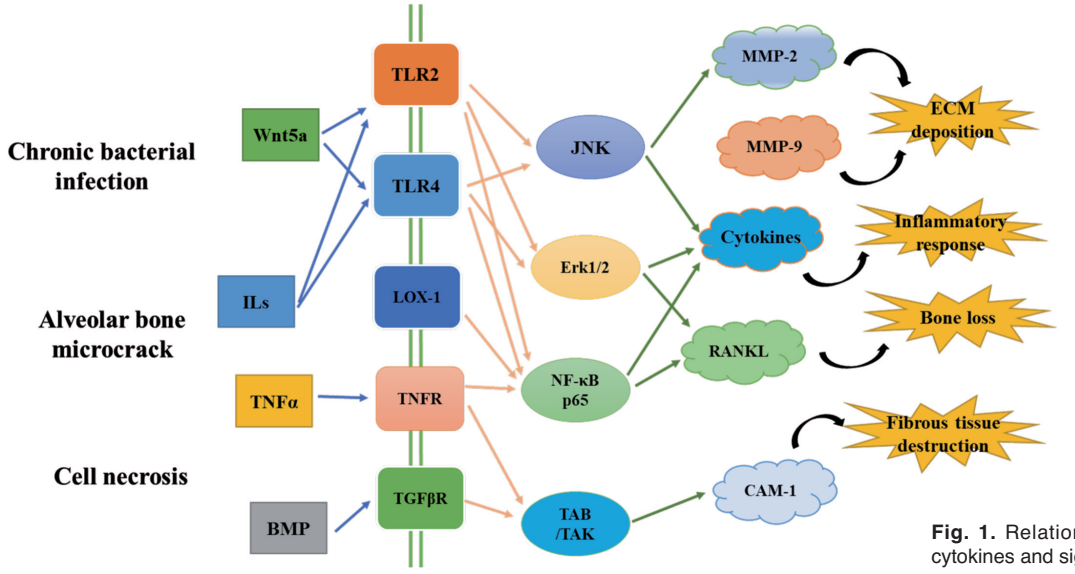

Fig. 1. Relationship between inflammation cytokines and signaling pathway in PMICF.

intercellular adhesion molecule 1 (sICAM-1) is another form of ICAM-1, which is a membrane-bound cytokine that is formed by the cleavage, cutting, and exfoliation of ICAM-1 on the surface of the cell membrane. sICAM-1 can mediate the directional migration of neutrophils and lymphocytes, infiltrate the surrounding connective tissues, and plays an essential role in the destruction of fibrous tissue and bone tissue in the process of inflammation around implants. It has been confirmed that sICAM-1 is expressed in the GCF regardless of the health status of natural periodontal tissues. The aggregation of plaques around miniscrew implants may lead to the up-regulation of ICAM-1 on the surface of junctional epithelium, gingival epithelium, and neutrophils, and ultimately up-regulation of sICAM-1 expression. In a study conducted by Huimin et al., the results showed that the expression of sICAM-1 was found in the fluids around the titanium anchorage nails of the micro-implant, whether it was loaded or not, indicating that there was an immune response in the host after micro-implant implantation. The fluid around the titanium anchorage nail of micro-implant comes from plasma and tissue fluid. The fluid volume and the sICAM-1 expression in the loose group were significantly higher than those in the stable group, which may be related to the tissue's inflammation around the micro-implant titanium anchorage nails. With the prolongation of the loading time of microimplant titanium anchorage nails, the volume of surrounding liquid and the sICAM-1 expression changed slightly in the microimplant titanium anchorage nail stable group, while it increased gradually in the microimplant titanium anchorage nail loosening group; the difference was significant ($P<0.05$). This might be due to the aggravation of the inflammation after inflammation tissue loading. In this case, the factors in peripheral fluid include not only plasma exudations but also the accumulation and exfoliation of inflammatory cells, leading to a significant increase in the level of sICAM-1. There was no individual study that showed that any signaling pathway regulates the level of sICAM-1 in PMICF, but sICAM-1was dependent on TLR-4 activation and produced by activation of MMP-9 in osteolysis and aseptic implant loosening (Anjum et al., 2016). In the ICAM-1/VCAM-1 dependent manner, synovial fibroblasts promoted the production of IL-17 induced by CD4 + T cells. However, the role of IL-17 and ICAM-1 in peri-implant inflammation has not been studied (Mori et al., 2017).

Conclusion and prospects

At present, most of the studies on biological factors affecting peri-miniscrew implant inflammation are clinical studies. PMICF and GCF are obtained from patients, and then the changes in biomarker levels relative to periodontal tissue metabolism are evaluated. These studies guide the prevention and treatment of peri-miniscrew implant inflammation. After miniscrew implant implantation, inflammation occurs in the surrounding tissue. Bacterial products implanted in the peri-implant sulcus have a chemotactic role in stimulating inflammatory factors and the implantation procedure also has a physical stimulation effect on soft tissue and hard tissue. Inflammatory factors cause inflammation in the surrounding tissues after implantation of peri-miniscrew implant and lead to anchorage screw shedding. Therefore, the expression of inflammatory factors and signaling pathways are critical in clinical orthodontics treatment.

We conclude that TLR-2, TLR-4, LOX-1, and BMP participate in the regulation of ILs (IL-1β, IL-6, IL-8, and IL-17), TNF-α, RANKL, MMP-2, MMP-9 expression via JNK, Erk1/2, Wnt5a, NF-kBp65, OPN, and TAB/TAK signaling pathway. Among them, IL-1β and IL-6 are the critical inflammation factors in the signaling pathway inducing the inflammatory reaction surrounding implants. Besides, CAM-1 was also regulated by MMP-9 and IL-17, but no other PMICF related studies, so it could be the potentially crucial factor in PMICF. Figure 1 shows that the inflammation cytokines surround PMICF and involving signaling pathways. And it has a reasonable reference value to the orthodontic force adjusted in time according to the levels of specific inflammatory factors. From the future direction of treatment, more suitable implant materials, implant surface treatment methods and control measures of the surrounding tissue environment can be selected according to the changes in the levels of these inflammatory factors. Attention should be paid to minimizing implant injury, maintaining good oral hygiene, increasing implant stability and improving efficiency.

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