Int J Clin Exp Pathol 2018;11(9):4283-4295
www.ijcep.com /ISSN:1936-2625/IJCEP0080308

Review Article

Resolution of inflammation in periodontitis: a review

Jing Huang[1*], Xinjie Cai[1,2*], Yanjing Ou[1], Yi Zhou[1,2], Yining Wang[1,2]

[1]The State Key Laboratory Breeding Base of Basic Science of Stomatology (Hubei-MOST) and Key Laboratory of Oral Biomedicine Ministry of Education, School and Hospital of Stomatology, Wuhan University, Wuhan 430079, China; [2]Department of Prosthodontics, Hospital of Stomatology, Wuhan University, Wuhan 430079, China. [*]Equal contributors.

Received May 25, 2018; Accepted August 15, 2018; Epub September 1, 2018; Published September 15, 2018

Abstract: Inflammation is a physiological response to an injury or infection. It is supposed to be self-limiting, stopping when the situation recovers to normal to protect the tissue. This self-limiting action is called "resolution of inflammation". Currently, periodontitis is thought to be the result of failed resolution of inflammation; specifically, it is the result of excessive inflammation that leads to gingival recession and alveolar bone loss. In this review, we will focus on the processes of resolution of inflammation in periodontitis, which may be a therapeutic target of periodontitis.

Keywords: Periodontitis, inflammation, self-limited, resolution

Introduction

Inflammation is assumed to occur to protect tissue that has been infected or injured. There are different results after the onset of an inflammatory response: ideally, the pathogenic stimuli are eliminated, and the tissues return to homeostasis, which is the optimal response; however, if the resolution process fails, the inflammation becomes uncontrolled and chronic [1]. Recently, it has become clear that the inflammatory process includes key checkpoints that regulate its onset, maintenance, and resolution [2, 3].

Periodontitis is globally prevalent and is the major cause of tooth loss in adults [4]. Over the last four decades, there is no evidence that the prevalence of periodontitis has changed over time [5]. Periodontitis is an inflammation induced by bacterial pathogens. It is characterized by gingival recession and alveolar bone loss [6]. Until now, the conventional therapy to periodontitis is scaling and root planning [7]. Nowadays it is recognized that the bacterial biofilm-induced body response is the essential cause of periodontal destruction during the pathogenesis of the disease [8]. It is now thought that periodontitis is the result of uncontrolled and unresolved inflammation [9, 10]. Therefore, we should more deeply examine the molecular and cellular mechanisms of inflammation resolution and target them to treat periodontitis. The resolution of inflammation in periodontitis should be an active process involving a series of cells and processes. Inflammation-induced recruitment of neutrophils should change to apoptosis in a timely manner. Pro-inflammation macrophages should be reprogrammed to become pro-resolution macrophages. Lymphangiogenesis and lymphatic function play a key role in the balance of inflammation in periodontitis. Regarding the adaptive immune responses, Treg cells are important for inhibiting excessive inflammation. More importantly, clinical trials show that pro-resolution mediators are effective for resolving periodontitis [11].

Neutrophil apoptosis

Neutrophils constitute 40-60% of the white blood cell population and form the body's first line of defense against invading pathogens, such as bacteria. They are the first leukocytes to enter the inflammatory site, and they can eliminate pathogens via multiple mechanisms, such as proteolytic enzymes, antimicrobial proteins and reactive oxygen species [12]. Under normal conditions, the longevity of neutrophils

is short, lasting approximately a few hours. During inflammation, the longevity of neutrophils increases because of their activation, which ensures that they participate in the inflammatory responses [13]. Neutrophils have been shown to be present in the inflamed periodontium, and chemotaxis disorders in neutrophils will increase the severity of periodontitis [14, 15].

However, the excessive presence of neutrophils will prolong the process of inflammation by continuing to produce antigens and secrete inflammatory cytokines and will damage the tissue by secreting protein enzymes and toxic oxygen [16]. Therefore, the timely apoptosis and phagocytosis of neutrophils is extremely important for resolving inflammation and restoring tissue. The morphology of apoptotic neutrophils is infrequently detected during the resolution stage [17]. Neutrophil apoptosis is mediated by various extrinsic and intrinsic factors; for example, cell-to-cell Fas/Fasl contact can induce apoptosis, and reactive oxygen species (ROS) from the NAPDH oxidase also limits the survival of neutrophils. Furthermore, some environmental circumstances, such as hypoxia, interfere with neutrophil longevity [3, 18, 19]. Apoptotic neutrophils are removed via efferocytosis, through which they are found and eaten by macrophages via specific signals. Lysophosphatidylcholine (LPC), sphingosine 1-phosphate (S1P), fractalkine (CX3CL1) help macrophages find apoptotic neutrophils. Phosphatidylserine (PS) is the signal that apoptotic neutrophils express to indicate that they should be eaten [3, 20]. Neutrophil apoptosis helps to resolve inflammation not only by decreasing the number of existing neutrophils but also by expressing signals that block the recruitment of more neutrophils and influence the function of other immune cells, such as annexin A1 and lactoferrin. The subsequent efferocytosis inhibits the secondary necrosis of neutrophils, which would otherwise release toxic granules and oxygen species and harm the tissue [19].

The study of apoptosis in periodontitis began a decade ago, but few later studies have been conducted. Gamonal and colleagues [21] demonstrated that the cytokines TNFα and GM-CSF were elevated in gingival crevicular fluid. In a later ex vivo gingival tissue biopsy culture, 100 ug/ml GM-CSF was added to the medium for 2 and 4 days. Apoptosis was measured using the terminal TdT-mediated Dutp-biotin nick-end labelling (TUNEL) technique, and Bax expression was observed by immunohistochemistry. The results showed that apoptosis was reduced in the GM-CSF treated gingiva. This research implied a novel mechanism of periodontitis in which GM-CSF-induced delays in neutrophil apoptosis contributed to the failed resolution of periodontitis. The results of a recent study were consistent with this conclusion [22]. Svetislav Zaric and colleagues found that P. gingivalis LPS could only induce partial immune tolerance in the human monocytic cell line THP-1 because although the secretion of TNFα was decreased, the production of IL-8 remained high after repeated LPS challenges. Furthermore, the incubation of neutrophils with the supernatant of monocytes with impaired immune tolerance displayed a high migration index and increased apoptosis. This result reinforced the belief that the delayed apoptosis of neutrophils prolongs the inflammation that characterizes periodontitis. Another study positively confirmed the importance of neutrophil apoptosis in periodontitis [24]. Isolated neutrophils were induced to apoptosis in vitro which was confirmed with Annexin V positivity and the loss of CD16 expression. Then, isolated monocytes were cultured with apoptotic neutrophils or fresh neutrophils or alone. All three groups were stimulated with P. gingivalis LPS. The ELISA results showed that IL-10 levels were increased and IL-1β levels were inhibited in the apoptotic neutrophil-treated group compared with the other groups. This study's results demonstrated a typical mechanism through which neutrophil apoptosis helps resolve inflammation by producing a signal to stimulate monocytes to produce pro-resolution cytokines and suppress pro-inflammatory cytokines. This suggests that neutrophil apoptosis may be a potential target for resolving periodontitis. Currently, there are several methods for modulating neutrophil apoptosis, such as the use of pharmacological inhibitors of cyclin-dependent kinases to drive neutrophil apoptosis [24, 25]. Targeting apoptosis-associated pathways is another means of promoting resolution. Pharmacological inhibitors of ERK1/2, which is involved in the MAPK signal pathway, suppress the production of neutrophil survival factors and indirectly increase the apoptosis of neutrophils, which helps to resolve inflammation [26].

Macrophage reprogramming

Macrophages exist in nearly all tissues in the human body. Under normal or inflammatory situations, the circulating peripheral blood mononuclear cells recruit into the tissues and differentiate into macrophages [27]. There are many specific types of macrophages in the corresponding tissues: osteoclasts in the bone, microglial cells in the central nervous system, Kupffer cells in the liver and others [28]. In contrast with the replenishment function exhibited by recruited monocytes, macrophages may represent a self-renewal feature similar to that of stem cell and may proliferate in the tissue once they are activated by a stimulus [29]. Regarding the periodontium, after stimulation by P. gingivalis, monocytes and macrophages are recruited to the periodontium, which results in periodontitis [6].

Because of their cellular differentiation, widespread tissue distribution and responsiveness to various endogenous and exogenous stimuli, macrophages have marked phenotypic heterogeneity [30]. The classically activated macrophages (AAM or M1) activated by T helper 1(Th1)-cytokine interferon-r represent the most common and best known type. The concept of alternatively activated macrophages (CAM or M2), which are stimulated by Th2-type cytokines, has gained attention in the past decades [31-34]. In 1992 [34], Simon Gordon and colleagues identified the alternatively activated macrophages stimulated by IL-4, which is significantly different from the macrophages classically activated by IFN-r. The alternatively activated macrophages have a higher level of macrophage mannose receptor and secrete lower amounts of inflammatory cytokines. In 1994 [35], Gordon reported another type of alternatively activating macrophage that was stimulated by IL-13. The classically activated macrophages have features that are quite different from those of the alternatively activated macrophages. In terms of cell morphology, M2 cells are elongated, while M1 cells are round and pancake-like [36]. In terms of function, M1 cells are pro-inflammatory, while M2 cells are pro-resolution and pro-healing [37]. because of their different functions, each cell type dominates different stages in the cascade of inflammation. From the onset to the peak of inflammation or injury, M1 cells are dominant. Then, as the process turns to the resolution of inflammation and the recovery of tissue, M1 cells engage in the phagocytosis of apoptotic cells and transfer the process to the M2 cells [2, 30]. The M1 cells' surface markers are CD68 and major histocompatibility complex-II, while the M2 cells' surface markers are CD163 and CD206. M1 cells secrete more pro-inflammatory cytokines, including TNF-α, iNOS and other, whereas M2 cells secrete more immunoregulative cytokines, such as Arginase-1 and the pro-healing cytokines IL-10 and TGF-β [38, 39]. Furthermore, considerable in vitro and in vivo evidence indicates that M2 cells interact with stem cells or stem cell-like cells and support their proliferation and differentiation, while the M1 cells do not. Conversely, stem cell transplantation into a microenvironment will promote the transfer of M1 cells to M2 cells and have a pro-healing role [40, 41].

We have always known that macrophages are amplified in periodontitis. However, little is known about the different macrophages involved in the process of periodontitis. Mariely Navarrete and colleagues used IFN-r, IL-6, IL-4 and FXIII-A as indirect markers of the classical and alternative macrophages to show that both of the cell types exist in the inflamed periodontium [42]. More recently [43], Roselind S. Lam and colleagues demonstrated that the ratio of M1/M2 was increased in a mouse model of periodontitis compared with the control group. Additionally, the M1-related cytokines and chemokines TNF-α and MIP are increased in the collected supernatants of peritoneal macrophages. Furthermore, the depletion of macrophages by clodronate liposomes significantly reduces macrophage infiltration and prevents P. gingivalis-induced bone resorption in mice. The results were consistent with another recent research that the M1-type markers outnumber the M2-type markers in both periodontium and serum in periodontitis mice compared to control mice [44]. Another in vitro study using coculture of oral commensals and pathogens with macrophages suggested that P. gingivalis, as an oral pathogen, may program macrophages to M1 and result in a pro-inflammatory environment [45]. These results prove the pro-inflammation nature of M1 in periodontitis and suggest that M2 would dominate M1 in the resolution of inflammation in periodontitis. The same group also tested the different responses

of M1 and M2 to P. gingivalis stimulation [46]. M1 and M2 cells were induced from murine bone marrow macrophages and then incubated with a low or high dose of P. gingivalis. In M1 cells, the high dose of P. gingivalis LPS significantly increased the expression of CD40, CD86, inducible nitric oxide synthase (iNOS) and nitric oxide (NO). As to M2 cells, P. gingivalis LPS lightly increased the expression of CD206 and YM-1 but did enhance arginase expression. The in vitro research implied that the various macrophages have different functions in the process of periodontitis. In the research by Qunzhou Zhang and colleagues [47], the mucosa of normal and periodontitis patients were collected and compared with that of patients with bisphosphonate-related osteonecrosis of the jaws. The results showed that the proportion of iNOS+ M1 cells was significantly higher than that of the normal group, but the proportion of CD206+ M2 cells was significantly lower than that of the normal group. The above-mentioned studies suggest that it is worthwhile to attempt to rescue periodontitis using an M2-based tissue engineer. Kara L. Spiller and colleagues confirmed that tissue engineering scaffolds primed with an M2-inducer showed a high capacity for vascularization, which is consistent with the pro-healing activity of M2 cells [48]. Anusuya Das and colleagues used nanofibers composed of an S1P receptor agonist to treat mandibular defects; they obtained better regeneration than when normal nanofibers were used because of the M2 cell recruitment associated with the S1P receptor agonist nanofibers [49]. In the attempt to improve the osseointegration of a nanostructured titanium surface of an oral implant, Qianli Ma demonstrated that mediation by macrophage polarization plays a key role. Titanium surfaces that can recruit more M2 cells will achieve better implant osseointegration [50].

Lymphangiogenesis and lymphatic function

The lymphatic system participates in the regulation of the microenvironment by returning proteins, cells, molecules and fluid to the circulating blood. Furthermore, it removes dead or mutant cells, microbes and foreign matter under pathogenic conditions [51, 52]. During the embryonic period, the formation of LVs is initiated from a subset of venous endothelial cells of the cardinal vein that express Prox-1. In adulthood, lymphangiogenesis will occur only under certain conditions, such as tissue injury, inflammation and tumors [53]. Lymphangiogensis and lymphatic function play a complex role in inflammation which is accompanied by vascular responses, migration and the activation of leukocytes. To relieve the inflammation, pathogens, debris and excessive inflammatory cells must be removed; thus, the need for appropriate lymphatic drainage arises under inflammatory conditions [54]. Lymphangiogensis is a context-dependent reaction that alters the process of inflammation and tissue repair. The most studied signaling pathway of inflammatory lymphangiogenesis is the vascular endothelial growth factor (VEGF)-C and VEGF receptor 3 pathway [55]. The VEGF-A and VEGF receptor 2 pathway is also known to contribute to inflammatory lymphangiogenesis. T cell-derived IFN-r is a vital anti-lymphangiogenic cytokine. During the development of inflammation, pro-lymphangiogenic factors overweigh anti-lymphatic factors, which results in an outburst of lymphatic vessels. When the inflammation process turns to resolution, the anti-lymphatic factors dominate, and the excessive lymphatic network regresses (54). The markers of mature LECs are Prox-1, VEGF-3, LYVE-1 and podoplanin. The lymph travels through different sizes of channels from the inflamed tissue to the blood circulation: lymph capillaries, collecting vessel, lymph nodes, lymphatic trunks and lymphatic ducts [56]. During the initiation of inflammation, lymphatic vessels recruit inflammatory cells from the circulatory system to the inflamed tissue and pass the antigen-loaded immune cells into the lymph nodes. The lymphatic vessels recruit CCR7+ dendritic cells and T and B cells by secreting CCL21 (also known as secondary lymphoid chemokine, SLC) [57]. Furthermore, the LECs themselves interact with immune cells and contribute to the peripheral tissue's inflammatory response. During the resolution of inflammation, the lymphatic vessels help drain away the apoptotic leukocytes, hostile debris, and fluid. Afterward, the additional lymphatic vessels should fade away and recover to normal levels. If they do not, the excess lymphatic vessels will cause unwanted inflammation by transporting antigens into the lymph nodes, and the immune response will continue. Thus, inflammation could be partially mediated by targeting lymphangiogenesis [54, 57].

To date, little attention is paid to the role of lymphatic vessels in oral tissue. Lymphatic vessels in the gingiva of mice were first described using lymphatic vessel endothelial hyaluronan receptor (LYVE)-1 as a specific marker [58, 59]. Under normal conditions, gingival lymphatic vessels are located in the lamina propria. In normal condition, lymphangiogenesis was recently observed after infection with P. gingivalis [57, 60, 61]. When the inflammation process began, both the number and the size of the lymphatic vessels increased. The number of VEGF-C+/CD45+ immune cells increased significantly, while there was no change in the VEGF-D/CD45+ cells [60]. This implies that VEGF-C might be mainly responsible for inflammatory lymphangiogenesis in periodontitis. The trapping of VEGF-C and D by soluble VEGFR-3 results in genetically modified K14-VEGFR3-Ig mice that are deficient in dermal and gingival lymphatic vessels [62]. However, the regression of inflammation is specific to the lymphatics because the blood vessel network does not seem to be influenced in this model. New mice models offer more opportunities to investigate lymphangiogenesis and its role in periodontal diseases. Lilian E. Mkonyi and colleagues observed that K14-VEGFR3-Ig mice developed more severe bone resorption than WT mice in a model of periodontitis induced by P. gingivalis [63]. The histological examination of the periodontal tissue revealed higher numbers of F4/80+ macrophages in the defects, and increased levels of the pro-inflammatory cytokines IFN-r, IL-1β, RANKL and M-CSF confirmed the presence of more serious inflammation. These cytokines are essential to the activation of osteoclasts. Furthermore, the production of antibody IgG to P. gingivalis was impaired, which implied an impaired humoral immune response. This may be the result of damaged gingival drainage following the reduced capacity of antigen-presenting cells to travel to the lymph nodes. The above-mentioned studies show that effective lymphangiogenesis is necessary for the resolution of inflammation. However, there is insufficient research regarding the role of excessive lymphangiogenesis in the uncontrolled inflammation of periodontitis, and translational research regarding lymphangiogenesis in human periodontitis is lacking. VEGF-C can significantly increase lymphangiogenesis, and anti-lymphatic treatment with anti-VEGFR-3 antibody (mF4-31C1) can inhibit additional lymphangiogenesis [54]. However, attention must be paid to the complexity and different contexts of lymphatic biology during treatment. Lymphatic target therapy could be a double-edged sword. Investigations of the lymphatic biology of the gingiva during inflammation will surely open a new window onto the pathogenesis of periodontitis. Translational research is worth conducting, as are therapeutic trials of lymphangiogenesis modulation in periodontitis.

Immune-suppressive Treg cells

Tregs are a subset of T lymphocytes that express CD4, CD25 and the transcription factor Foxp3 and have an immune suppression feature. They are important for ensuring immune homeostasis to prevent T cell-induced immune responses from damaging the host [64]. Treg cells include natural Tregs (nTregs) and inducible Tregs (iTregs). The two types of Tregs differ in terms of development and function. nTregs reside in the thymus and constitute 5-10% of the naïve CD4+ T cells pool in normal individuals. iTregs are driven by naïve T cells primed by IL-10 and TGF-β in the peripheral tissues. nTregs play a role in immune homeostasis via cell contact, while iTreg cells mediate the immune response by secreting suppressive cytokines [65]. Treg cells limit chronic inflammation by suppressing and regulating the T helper cells. In addition, Treg cells can exert immune-regulatory functions independent of inhibiting Th cells [66]. In Rag1-/- mice, which lack T and B cells, the transfer of Treg cells can eliminate lung inflammation by inducing alveolar neutrophil apoptosis and macrophage efferocytosis, thus decreasing the level of pro-inflammatory cytokines. Furthermore, Tregs play a role in bone biology. Emerging evidence shows the inhibition of Treg cells during osteoclastogenesis. Treg cells can inhibit osteoclastogenesis and the formation of osteoclasts via the secretion of IL-10, TGF-β and IL-4. Cell-to-cell contact via cytotoxic T lymphocyte antigen 4 (CTLA4) also plays a role [67]. In a pilot study including 7 subjects with healthy gingiva and 8 with chronic periodontitis, a higher proportion of CD4+CD25+Foxp3+CD45RB+ Treg in the peripheral blood samples of chronic periodontitis subjects compared to that of healthy ones [68].

Because of the immune modulation potential of Tregs, they are considered a promising immunotherapy source for several immune-related diseases [69]. The transfer of autologous Treg cells is relatively easy and generally includes a protocol of isolation, enrichment and re-infusion. Other strategies that aim to induce Treg cells in vivo, such as the injection of IL-2, have also been studied. A third method for Treg therapy is the conversion of antigen-specific conventional T cells to Treg cells, although this process is characterized by many uncertainties [70]. It is clear that Treg cells are present in periodontitis [71]; furthermore, they are observed during later stages of the disease. R. Kobayashi and colleagues demonstrated that IL-10+CD4+ T cells are increased in the inflamed gingiva, as are CD4+CD25+Foxp3+ T cells during the late period of P. gingivalis infection [72]. Garlet GP and colleagues [73] demonstrated progressive alveolar bone loss 15 days post-infection in a model of A. actinomycetemcomitans-induced periodontitis, while CD4+Foxp3+ Treg cells were only observed 30 days pi. The levels of IL-10 and CTLA-4 were positively correlated with the number of Treg cells. However, the Treg cells were decreased in the anti-GITR group, the severity of alveolar bone loss increased 30 days pi, and the infiltration of inflammatory cells was increased. However, periodontal infection control was not affected because the level of A. actinomycetemcomitans in the periodontal tissue and the level of serum CRP were not influenced. The researchers concluded that the protective mechanism of Treg cells in periodontitis was related to the secretion of CTLA-4, TGF-β, and IL-10. In another study [74], C-C motif chemokine ligand 22 (CCL22) was made into a degradable polymer, poly lactic-co-glycolic acid (PLGA). CCL22-releasing microparticles were injected into the local gingiva of mice in a mouse periodontitis model. The measurements of the area between the cementoenamel junction and the alveolar bone crest were decreased 10 days pi in the CCL22 group. The mechanism for this decrease was the recruitment of Treg cells because CCL22 is the ligand of CCR4, which is highly expressed in Treg cells. The mice that received CCL22-releasing microparticles expressed higher levels of the Treg cells markers. The levels of the pro-inflammatory cytokines were down-regulated. The transgenic CCR4ko mice showed significant impairment in Treg cells migration, which resulted in increased alveolar bone loss and higher pro-inflammatory cytokine levels. Another ex vivo study [75] showed that CD4+CD25+ Treg cells could affect the antimicrobial response and inhibit reactive oxygen and pro-inflammatory cytokines. Furthermore, Tregs can reverse the survival of neutrophils and promote their apoptosis. These results provide direct evidence of the pro-resolution feature of Treg cells and show the important roles of Treg cells in the resolution of periodontitis. The recruitment or enrichment of Treg cells may be a promising treatment for periodontitis.

Induction of pro-resolution mediators

At present, the most attractive pro-resolution mediators are a number of lipid mediators derived from polyunsaturated fatty acids (PUFAs). These include lipoxin (LX), resolvin (Rv)-D, resolvin-E, protectin, maresin [76-78]. Lipoxins are derived from the omega-6 polyunsaturated fatty acid arachidonic acid. LXs are produced quickly and work in a paracrine or autocrine manner [79]. LipoxinA4 (LXA4) works by binding to its high-affinity receptor formyl-peptide receptor2/lipoxin A4 receptor (ALX/FPR2), which belongs to the formyl peptide receptor superfamily [80]. In addition, recent data demonstrated that LXA4 shares GPR32 with another pro-resolution mediator, Resolvin D1 [81]. The most frequently recognized mechanism involved in the inflammation resolution ability of LXs is their ability to prevent the recruitment of neutrophils [82]. However, LXs can also upregulate the phagocytosis of apoptotic neutrophils by macrophages, which might stimulate the alternative activation of macrophages [83, 84]. In the research by Souza et al. [85], 15-epi-lipoxin A4 accompanied by an annexin-1-derived peptide can prevent TNF-α production and alleviate inflammation in a manner similar to that of IL-10, another inflammation modulating cytokine. Another study [86] demonstrated that LXA4 induced the expression of suppressor of cytokine signaling (SOCS)-2 via AhR and LXAR in dendritic cells and served to down-regulate inflammation. In the recent study by Emma Borgeson and colleagues [87], LXA4 had a protective role in P. gingivalis-induced inflammation; by inhibiting the Rho GTPase-signal pathway and decreasing CD11b/CD18, LXA4 prevented P. gingivalis-

induced cell activation. Furthermore, LXA4 also decreased the aggregation and ROS in the whole blood, which is important for the prevention of some forms of general periodontitis-related inflammation, such as atherosclerosis. T. E. Van Dyke's group demonstrated [88] the pro-resolution feature of a novel lipoxin analogue (benzo-lipoxin A4, bLXA4) in a miniature pig model of periodontitis. To imitate the endogenous relief provided by lipoxin, they used bLXA4-contaning nano-pro-resolving medicines (NPRM) to treat periodontal defects. The results showed a dramatic regeneration of hard and soft tissues, and the histological results confirmed the decreased infiltration of inflammatory cells.

Resolvins and protectins are derived from omega-3 polyunsaturated fatty acids. There are two forms of resolvins: D and E [89]. ChemR23 is the first receptor identified for RvE1. RvD1 binds to two GPCRs: ALX and GPR32 [90]. Similar to LXA4, RvE1 and RvD1 can stop PMN infiltration and promote macrophages' phagocytosis of apoptotic neutrophils [91, 92]. RvD1 was proven to contribute to the alternative activation of macrophages [93], and RvE1 could induce the apoptosis of activated CD4+ T cells, which is an important step in the resolution of inflammation [93]. The role of Rv in the resolution of periodontitis has been confirmed by several studies. Hatice Hasturk et al. [94] applied 4 μg of RvE1 per tooth in a model of ligature- and P. gingivalis-induced periodontitis in rabbits. The treatment was administered three times per week for 6-week period. Quantitative morphologic study showed that the RvE1 application regenerated periodontitis-related bone loss to pre-disease levels, and the clinical periodontitis parameters were all improved. Histological evaluation showed a significant elimination of inflammatory cells in the RvE1 group. Hard tissue slices demonstrated a recovery of the periodontal ligament, cementum, and alveolar bone. The TRAP-stained sections confirmed a low number of osteoclasts in the RvE1 group, and the RvE1 group showed much lower levels of serum CRP and IL-1β. This series of data showed the full range of periodontitis resolution and regeneration induced by RvE1. Another study showed a similar result, and a binding experiment showed that RvE1 specifically binds to neutrophils [95]. Li Gao et al. [96] found that alveolar bone loss was decreased in ligature-induced periodontitis, and leukocytes were cleared in the peritoneal cavity of transgenic mice that overexpressed the RvE1 receptor chemR23. In vitro bone cultures exposed to RvE1 showed increased expression of osteoprotegerin (OPG). In another in vitro culture, osteoclasts were limited in the presence of RvE1, and resorption pit formation was decreased [97]. Similarly, RvD1 down-regulated P. gingivalis-induced inflammation by eliminating pro-inflammatory cytokines such as IL-6 and monocyte chemotactic protein (MCP)-1 in human gingival fibroblasts; furthermore, RvD1 had a positive effect on cell survival [98]. In addition to local application, omega-3 polyunsaturated fatty acids have also been administered via the diet [99]. In a parallel-design, double-blind clinical trial, eighty patients with chronic periodontitis were assigned to two treatment groups, one that underwent conventional scaling and root planing with a placebo and another that underwent scaling and root planing with the addition of dietary fish oil (900 mg eicosapentaenoic acid and docosahexaenoic acid) and 81 mg aspirin. The results showed that probing depth was decreased in the omega-3 group compared with the conventional group, and the salivary RANKL and MMP-8 concentrations were reduced. In a more recent study, administration of Maresin 1 at 1 nM enhanced macrophage phagocytosis and bacterial killing of periodontal pathogens [100].

Several other molecules have the potential to mediate the resolution of inflammation. H_2O_2 has been shown to resolve inflammation by clearing neutrophils by both pharmacological and genetic means. In transgenic gp91phox-/- mice, the recruitment of neutrophils was not affected, but clearance was delayed. A low dose of H_2O_2 at the peak of inflammation induced the apoptosis of neutrophils [101]. Low concentrations of H_2O_2 have been shown to promote the proliferation of periodontal ligament fibroblasts and increase their osteoblastic differentiation [102]. However, a low concentration of H_2O_2 should be used to resolve periodontitis because high concentrations of H_2O_2 have been shown to be pro-inflammatory by inducing IL-8 [103]. TNFRs have four cysteine-rich domains (CDR). CDR1 does not mediate the function of TNF-α immediately, but it plays a role in prompting TNFRs to form polymers; thus, it is called a pre-ligand-binding assembly

domain (PLAD) [104]. TNFR1-PLAD can bind to TNFR1 and block the combination of sTNFα and TNFR1. Additionally, TNFR1-PLAD can inhibit the nuclear movement of NF-κb [105]. TNFR1-PLAD has a potential application for the resolution of periodontitis, which we are exploring in our current research.

Discussion

The identification of inflammatory resolution as an active process has improved our understanding of the cascade of inflammation. Inflammation is necessary for the body to fight pathogenic invaders and keep the tissue intact; however, once the threat is past, the process is supposed to move to the resolution stage [106]. Failure of the resolution of inflammation leads to prolonged and chronic inflammation [107]. During the resolution stage, a series of processes occur and interact with each other. First, the pro-inflammatory chemokines cease production and become depleted, which leads to the blockage of neutrophil infiltration. Apoptosis is then induced in the existing neutrophils. Neutrophil apoptosis is central to the resolution of inflammation and influences the features of other immune cells. Macrophages engage in efferocytosis of the apoptotic neutrophils and transfer to alternatively activated macrophages. AAM is characterized by pro-resolution and pro-healing cells. Excessive immune cells and pathogens are drained to the circulatory system through the lymphatic system. However, lymphogenesis is supposed to be blocked in a timely manner to avoid the uncontrolled production of antigens. In the adoptive immune system, Treg cells can limit the other Th cells and produce some rehabilitative cytokines. Furthermore, many autologous lipids and cytokines have the potentials to resolve the inflammation.

Periodontitis is an excessive inflammation caused by microbial biofilm and the host immune response [108]. It is thought that periodontitis is a result of the failed resolution of inflammation in the periodontium. Any mistake in inflammation resolution process described above may lead to the prolonged inflammation and tissue destruction of periodontitis. Preprogrammed neutrophil apoptosis is delayed, which gives neutrophils an opportunity to promote excessive inflammation and destroy the tissue. The dominant macrophages in periodontitis are classically activated macrophages that do not successfully transition to alternatively activated macrophages. Lymphangiogenesis is indispensable to the resolution of periodontitis; without it, the periodontitis will become more serious. Regulatory T cells are shown to help heal periodontitis and eliminate inflammation. Many pro-resolution lipids are used to cure periodontitis and exhibit considerable potential for resolution based on their observed tissue regeneration and decreased inflammation.

Despite our progress in the area of resolution, additional work must be performed; in particular, we need more in-depth research into the various processes involved in the resolution of periodontitis and the specific methods that can influence them in an ideal direction. Future studies should examine how we can specifically induce neutrophil apoptosis without influencing other types of cells, whether there any methods that can help M1 transition to M2, and whether M2-based tissue engineering can help resolve periodontitis. Lymphangiogenesis is a complex biological process, and translational research is needed in this new field. Further trial modulations of lymphangiogenesis should be performed. Recruiting Treg cells to the inflammation site seems to offer potential for resolving periodontitis. At present, many lipids and cytokines have demonstrated usefulness for resolving periodontitis, and the field is still active.

Acknowledgements

This work was partly supported by National Natural Science Foundation of China (No. 81571011, 81371170, 81500888 and 81200812), Fundamental Research Funds for the Central Universities (No. 2042017kf0075), Hubei Provincial Natural Science Foundation of China (No. 2017CFB183) and Wuhan Science and Technology Project (No. 201606010101-0043).

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Yi Zhou and Yining Wang, The State Key Laboratory Breeding Base of Basic Science of Stomatology (Hubei-MOST) and Key Laboratory of Oral Biomedicine Ministry of Education, School and Hospital of Stomatology,

Wuhan University, Wuhan 430079, China. Tel: +86 27 87686318; Fax: +86 27 87873260; E-mail: dryizhou@whu.edu.cn (YZ); wang.yn@whu.edu.cn (YN-W)

References

[1] Perez DA, Vago JP, Athayde RM, Reis AC, Teixeira MM, Sousa LP, Pinho V. Switching off key signaling survival molecules to switch on the resolution of inflammation. Mediators Inflamm 2014; 2014: 829851.

[2] Alessandri AL, Sousa LP, Lucas CD, Rossi AG, Pinho V, Teixeira MM. Resolution of inflammation: mechanisms and opportunity for drug development. Pharmacol Ther 2013; 139: 189-212.

[3] Ortega-Gomez A, Perretti M, Soehnlein O. Resolution of inflammation: an integrated view. EMBO Mol Med 2013; 5: 661-74.

[4] Slots J. Periodontitis: facts, fallacies and the future. Periodontol 2000 2017; 75: 7-23.

[5] Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich T. Global epidemiology of dental caries and severe periodontitis-a comprehensive review. J Clin Periodontol 2017; 44 Suppl 18: S94-S105.

[6] Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. Periodontol 2000 2014; 64: 57-80.

[7] Preus HR, Gjermo P, Baelum V. A randomized double-masked clinical trial comparing four periodontitis treatment strategies: 5-year tooth loss results. J Periodontol 2017; 88: 144-52.

[8] Hajishengallis G. Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response. Trends Immunol 2014; 35: 3-11.

[9] Van Dyke TE. Proresolving lipid mediators: potential for prevention and treatment of periodontitis. J Clin Periodontol 2011; 38 Suppl 11: 119-25.

[10] Thomas MV, Puleo DA. Infection, inflammation, and bone regeneration: a paradoxical relationship. J Dent Res 2011; 90: 1052-61.

[11] Haworth O, Buckley CD. Resolving the problem of persistence in the switch from acute to chronic inflammation. Proc Natl Acad Sci U S A 2007; 104: 20647-8.

[12] Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A. Neutrophil function: from mechanisms to disease. Annu Rev Immunol 2012; 30: 459-89.

[13] Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol 2013; 13: 159-75.

[14] Srinivasan PC. Neutrophils-the sentinels of periodontal innate immunity. J Clin Cell Immunol 2013; 2013: 2.

[15] Mârțu I, Ursache M, Mârțu S, Luchian I, Costuleanu M. Evaluation neutrophil chemotaxis dysfunction to aggressive and chronic periodontitis. Romanian Journal of Oral Rehabilitation 2012; 4: 9-15.

[16] Wright HL, Moots RJ, Bucknall RC, Edwards SW. Neutrophil function in inflammation and inflammatory diseases. Rheumatology 2010; 49: 1618-31.

[17] Bratton DL, Henson PM. Neutrophil clearance: when the party is over, clean-up begins. Trends Immunol 2011; 32: 7.

[18] O'Donnell JA, Kennedy CL, Pellegrini M, Nowell CJ, Zhang JG, O'Reilly LA, Cengia L, Dias S, Masters SL, Hartland EL, Roberts AW, Gerlic M, Croker BA. Fas regulates neutrophil lifespan during viral and bacterial infection. J Leukoc Biol 2015; 97: 321-6.

[19] Fox S, Leitch AE, Duffin R, Haslett C, Rossi AG. Neutrophil apoptosis: relevance to the innate immune response and inflammatory disease. J Innate Immun 2010; 2: 216-27.

[20] Kennedy AD, DeLeo FR. Neutrophil apoptosis and the resolution of infection. Immunol Res 2009; 43: 25-61.

[21] Gamonal J, Sanz M, O'Connor A, Acevedo A, Suarez I, Sanz A, Martínez B, Silva A. Delayed neutrophil apoptosis in chronic periodontitis patients. J Clin Periodontol 2003; 30: 616-23.

[22] Zaric S, Shelburne C, Darveau R, Quinn DJ, Weldon S, Taggart CC, Coulter WA. Impaired immune tolerance to porphyromonas gingivalis lipopolysaccharide promotes neutrophil migration and decreased apoptosis. Infect Immun 2010; 78: 4151-6.

[23] Berker E, Kantarci A, Hasturk H, Van Dyke TE. Effect of neutrophil apoptosis on monocytic cytokine response to porphyromonas gingivalis lipopolysaccharide. J Periodontol 2005; 76: 964-71.

[24] Rossi AG, Sawatzky DA, Walker A, Ward C, Sheldrake TA, Riley NA, Caldicott A, Martinez-Losa M, Walker TR, Duffin R, Gray M, Crescenzi E, Martin MC, Brady HJ, Savill JS, Dransfield I, Haslett C. Cyclin-dependent kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cell apoptosis. Nat Med 2006; 12: 1056-64.

[25] Sekine C, Sugihara T, Miyake S, Hirai H, Yoshida M, Miyasaka N, Kohsaka H. Successful treatment of animal models of rheumatoid arthritis with small-molecule cyclin-dependent kinase inhibitors. J Immunol 2008; 180: 1954-61.

[26] Sawatzky DA, Willoughby DA, Colville-Nash PR, Rossi AG. The involvement of the apoptosis-

modulating proteins ERK 1/2, Bcl-xL and Bax in the resolution of acute inflammation in vivo. Am J Pathol 2006; 168: 33-41.
[27] Pola C. Monocytes and macrophages: tissue control of macrophages. Nat Med 2014; 20: 594-5.
[28] Stout RD, Suttles J. Functional plasticity of macrophages: reversible adaptation to changing microenvironments. J Leukoc Biol 2004; 76: 509-13.
[29] Sieweke MH, Allen JE. Beyond stem cells: self-renewal of differentiated macrophages. Science 2013; 342: 946-53.
[30] Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Front Biosci 2008; 13: 453-61.
[31] Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008; 8: 958-69.
[32] Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nat Rev Immunol 2005; 5: 953-64.
[33] Gordon S. Alternative activation of macrophages. Nat Rev Immunol 2003; 3: 23-35.
[34] Stein M, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. J Exp Med 1992; 176: 287-92.
[35] Doyle AG, Herbein G, Montaner LJ, Minty AJ, Caput D, Ferrara P, Gordon S. Interleukin-13 alters the activation state of murine macrophages in vitro: comparison with interleukin-4 and interferon-gamma. Eur J Immunol 1994; 24: 1441-5.
[36] McWhorter FY, Wang T, Nguyen P, Chung T, Liu WF. Modulation of macrophage phenotype by cell shape. Proc Natl Acad Sci U S A 2013; 110: 17253-8.
[37] Varin A, Gordon S. Alternative activation of macrophages: immune function and cellular biology. Immunobiology 2009; 214: 630-41.
[38] Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000 prime Reports 2014; 6: 13.
[39] Chazaud B. Macrophages: supportive cells for tissue repair and regeneration. Immunobiology 2014; 219: 172-8.
[40] Freytes DO, Kang JW, Marcos-Campos I, Vunjak-Novakovic G. Macrophages modulate the viability and growth of human mesenchymal stem cells. J Cell Biochem 2013; 114: 220-9.
[41] Cho DI, Kim MR, Jeong HY, Jeong HC, Jeong MH, Yoon SH, Kim YS, Ahn Y. Mesenchymal stem cells reciprocally regulate the M1/M2 balance in mouse bone marrow-derived macrophages. Exp Mol Med 2014; 46: e70.
[42] Navarrete M, Garcia J, Dutzan N, Henríquez L, Puente J, Carvajal P, Hernandez M, Gamonal J. Interferon-gamma, interleukins-6 and -4, and factor XIII-A as indirect markers of the classical and alternative macrophage activation pathways in chronic periodontitis. J Periodontol 2014; 85: 751-60.
[43] Lam RS, O'Brien-Simpson NM, Lenzo JC, Holden JA, Brammar GC, Walsh KA, McNaughtan JE, Rowler DK, Van Rooijen N, Reynolds EC. Macrophage depletion abates porphyromonas gingivalis-induced alveolar bone resorption in mice. J Immunol 2014; 193: 2349-62.
[44] Yu T, Zhao L, Huang X, Ma C, Wang Y, Zhang J, Xuan D. Enhanced activity of the macrophage M1/M2 phenotypes and phenotypic switch to M1 in periodontal infection. J Periodontaol 2016; 87: 1092-102.
[45] Huang CB, Alimova Y, Ebersole JL. Macrophage polarization in response to oral commensals and pathogens. Pathog Dis 2016; 74.
[46] Holden JA, Attard TJ, Laughton KM, Mansell A, O'Brien-Simpson NM, Reynolds EC. Porphyromonas gingivalis LPS weakly activates M1 and M2 polarised mouse macrophages but induces inflammatory cytokines. Infect Immun 2014; 82: 4190-4203.
[47] Zhang Q, Atsuta I, Liu S, Chen C, Shi S, Shi S, Le AD. IL-17-mediated M1/M2 macrophage alteration contributes to pathogenesis of bisphosphonate-related osteonecrosis of the jaws. Clin Cancer Res 2013; 19: 3176-88.
[48] Spiller KL, Anfang RR, Spiller KJ, Ng J, Nakazawa KR, Daulton JW, Vunjak-Novakovic G. The role of macrophage phenotype in vascularization of tissue engineering scaffolds. Biomaterials 2014; 35: 4477-88.
[49] Das A, Segar CE, Hughley BB, Bowers DT, Botchwey EA. The promotion of mandibular defect healing by the targeting of S1P receptors and the recruitment of alternatively activated macrophages. Biomaterials 2013; 34: 9853-62.
[50] Ma QL, Zhao LZ, Liu RR, Jin BQ, Song W, Wang Y, Zhang YS, Chen LH, Zhang YM. Improved implant osseointegration of a nanostructured titanium surface via mediation of macrophage polarization. Biomaterials 2014; 35: 9853-67.
[51] Alitalo K. The lymphatic vasculature in disease. Nat Med 2011; 17: 1371-80.
[52] Alitalo K, Tammela T, Petrova TV. Lymphangiogenesis in development and human disease. Nature 2005; 438: 946-53.
[53] Kim H, Kataru RP, Koh GY. Regulation and implications of inflammatory lymphangiogenesis. Trends Immunol 2012; 33: 350-6.
[54] Kim H, Kataru RP, Koh GY. Inflammation-associated lymphangiogenesis: a double-edged sword? J Clin Invest 2014; 124: 936-42.

[55] Zheng W, Aspelund A, Alitalo K. Lymphangiogenic factors, mechanisms, and applications. Periodontol 2000 2014; 124: 878-87.
[56] Tammela T, Alitalo K. Lymphangiogenesis: molecular mechanisms and future promise. Cell 2010; 140: 460-76.
[57] Berggreen E, Wiig H. Lymphangiogenesis and lymphatic function in periodontal disease. J Dent Res 2013; 92: 1074-80.
[58] Ushijima N, Inoue K, Domon T, Yoshida S. Distribution and organization of lymphatic vessels in the mouse gingiva: an immunohistochemical study with LYVE-1. Arch Oral Biol 2008; 53: 652-8.
[59] Berggreen E, Haug SR, Mkonyi LE, Bletsa A. Characterization of the dental lymphatic system and identification of cells immunopositive to specific lymphatic markers. Eur J Oral Sci 2009; 117: 34-42.
[60] Mkonyi LE, Bakken V, Sovik JB, Mauland EK, Fristad I, Barczyk MM, Bletsa A, Berggreen E. Lymphangiogenesis is induced during development of periodontal disease. J Dent Res 2012; 91: 71-7.
[61] Berggreen E, Wiig H. Lymphatic function and responses in periodontal disease. Exp Cell Res 2014; 325: 130-7.
[62] Mkonyi LE, Bletsa A, Fristad I, Wiig H, Berggreen E. Importance of lymph vessels in the transcapillary fluid balance in the gingiva studied in a transgenic mouse model. Am J Physiol Heart Circ Physiol 2010; 299: H275-H283.
[63] Mkonyi LE, Bletsa A, Bolstad AI, Bakken V, Wiig H, Berggreen E. Gingival lymphatic drainage protects against Porphyromonas gingivalis-induced bone loss in mice. Am J Pathol 2012; 181: 907-16.
[64] Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell 2008; 133: 775-87.
[65] Yuan FL, Li X, Lu WG, Xu RS, Zhao YQ, Li CW, Li JP, Chen FH. Regulatory T cells as a potent target for controlling bone loss. Biochem Biophys Res Commun 2010; 402: 173-6.
[66] D'Alessio FR, Tsushima K, Aggarwal NR, West EE, Willett MH, Britos MF, Pipeling MR, Brower RG, Tuder RM, McDyer JF, King LS. CD4+ CD25+Foxp3+ Tregs resolve experimental lung injury in mice and are present in humans with acute lung injury. J Clin Invest 2009; 119: 2898-913.
[67] Zaiss MM, Axmann R, Zwerina J, Polzer K, Gückel E, Skapenko A, Schulze-Koops H, Horwood N, Cope A, Schett G. Treg cells suppress osteoclast formation: a new link between the immune system and bone. Arthritis Rheum 2007; 56: 4104-12.
[68] Sabarish R, Rao SR, Lavu V. Natural Natural T Regulatory Cells (n Treg) in the perpheral blood of healthy subjects and subjects with chronic periodontitis-a pilot study. J Clin Diagn Res 2016; 10: ZC36-9.
[69] Singer BD, King LS, D'Alessio FR. Regulatory T cells as immunotherapy. Front Immunol 2014; 5: 46.
[70] Miyara M, Ito Y, Sakaguchi S. Treg-cell therapies for autoimmune rheumatic diseases. Nat Rev Rheumatol 2014; 10: 543-51.
[71] Parachuru VPB, Coates DE, Milne TJ, Hussaini HM, Rich AM, Seymour GJ. Forkhead box P3-positive regulatory T-cells and interleukin 17-positive T-helper 17 cells in chronic inflammatory periodontal disease. J Periodontal Res 2014; 49: 817-826.
[72] Kobayashi R, Kono T, Bolerjack BA, Fukuyama Y, Gilbert RS, Fujihashi K, Ruby J, Kataoka K, Wada M, Yamamoto M, Fujihashi K. Induction of IL-10-producing CD4(+) T-cells in chronic periodontitis. J Dent Res 2011; 90: 653-8.
[73] Garlet GP, Cardoso CR, Mariano FS, Claudino M, de Assis GF, Campanelli AP, Avila-Campos MJ, Silva JS. Regulatory T cells attenuate experimental periodontitis progression in mice. J Clin Periodontol 2010; 37: 591-600.
[74] Glowacki AJ, Yoshizawa S, Jhunjhunwala S, Vieira AE, Garlet GP, Sfeir C, Little SR. Prevention of inflammation-mediated bone loss in murine and canine periodontal disease via recruitment of regulatory lymphocytes. Proc Natl Acad Sci U S A 2013; 110: 18525-30.
[75] Lewkowicz P, Lewkowicz N, Sasiak A, Tchórzewski H. Lipopolysaccharide-activated CD4+ CD25+ T regulatory cells inhibit neutrophil function and promote their apoptosis and death. J Immunol 2006; 177: 7155-63.
[76] Yates CM, Calder PC, Rainger GE. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. Pharmacol Ther 2014; 141: 272-82.
[77] Serhan CN, Chiang N. Resolution phase lipid mediators of inflammation: agonists of resolution. Curr Opin Pharmacol 2013; 13: 632-40.
[78] Im DS. Omega-3 fatty acids in anti-inflammation (pro-resolution) and GPCRs. Prog Lipid Res 2012; 51: 232-7.
[79] Ryan A, Godson C. Lipoxins: regulators of resolution. Curr Opin Pharmacol 2010; 10: 166-72.
[80] Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, Parmentier M, Serhan CN, Murphy PM. International union of basic and clinical pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. Pharmacol Rev 2009; 61: 119-61.
[81] Krishnamoorthy S, Recchiuti A, Chiang N, Yacoubian S, Lee CH, Yang R, Petasis NA, Serhan CN. Resolvin D1 binds human phagocytes with evidence for proresolving receptors. Proc Natl Acad Sci U S A 2010; 107: 1660-5.

[82] Fierro IM, Colgan SP, Bernasconi G, Petasis NA, Clish CB, Arita M, Serhan CN. Lipoxin A4 and aspirin-triggered 15-epi-lipoxin A4 inhibit human neutrophil migration: comparisons between synthetic 15 epimers in chemotaxis and transmigration with microvessel endothelial cells and epithelial cells. J Immunol 2003; 170: 2688-94.

[83] Godson C, Mitchell S, Harvey K, Petasis NA, Hogg N, Brady HR. Cutting edge: lipoxins rapidly stimulate nonphlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages. J Immunol 2000; 164: 1663-67.

[84] Maderna P, Godson C. Taking insult from injury: Lipoxins and Lipoxin receptor agonists and phagocytosis of apoptotic cells. Prostaglandins Leukot Essent Fatty Acids 2005; 73: 179-87.

[85] Souza DG, Fagundes CT, Amaral FA, Cisalpino D, Sousa LP, Vieira AT, Pinho V, Nicoli JR, Vieira LQ, Fierro IM, Teixeira MM. The required role of endogenously produced lipoxin A4 and annexin-1 for the production of IL-10 and inflammatory hyporesponsiveness in mice. J Immunol 2007; 179: 8533-43.

[86] Machado FS, Johndrow JE, Esper L, Dias A, Bafica A, Serhan CN, Aliberti J. Anti-inflammatory actions of lipoxin A4 and aspirin-triggered lipoxin are SOCS-2 dependent. Nat Med 2006; 12: 330-4.

[87] Borgeson E, Lonn J, Bergstrom I, Brodin VP, Ramström S, Nayeri F, Särndahl E, Bengtsson T. Lipoxin A(4) inhibits porphyromonas gingivalis-induced aggregation and reactive oxygen species production by modulating neutrophil-platelet interaction and CD11b expression. Infect Immun 2011; 79: 1489-97.

[88] Van Dyke TE, Hasturk H, Kantarci A, Freire MO, Nguyen D, Dalli J, Serhan CN. Proresolving nanomedicines activate bone regeneration in periodontitis. J Dent Res 2015; 94: 148-56.

[89] Serhan CN, Petasis NA. Resolvins and protectins in inflammation resolution. Chem Rev 2011; 111: 5922-43.

[90] Schwab JM, Chiang N, Arita M, Serhan CN. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. Nature 2007; 447: 869-74.

[91] Hong S, Lu Y. Omega-3 fatty acid-derived resolvins and protectins in inflammation resolution and leukocyte functions: targeting novel lipid mediator pathways in mitigation of acute kidney injury. Front Immunol 2013; 4: 13.

[92] Campbell EL, Louis NA, Tomassetti SE, Canny GO, Arita M, Serhan CN, Colgan SP. Resolvin E1 promotes mucosal surface clearance of neutrophils: a new paradigm for inflammatory resolution. FASEB J 2007; 21: 3162-70.

[93] Hsiao HM, Sapinoro RE, Thatcher TH, Croasdell A, Levy EP, Fulton RA, Olsen KC, Pollock SJ, Serhan CN, Phipps RP, Sime PJ. A novel anti-inflammatory and pro-resolving role for resolvin D1 in acute cigarette smoke-induced lung inflammation. PLoS One 2013; 8: e58258.

[94] Hasturk H, Kantarci A, Goguet-Surmenian E, Blackwood A, Andry C, Serhan CN, Van Dyke TE. Resolvin E1 regulates inflammation at the cellular and tissue level and restores tissue homeostasis in vivo. J Immunol 2007; 179: 7021-9.

[95] Hasturk H, Kantarci A, Ohira T, Arita M, Ebrahimi N, Chiang N, Petasis NA, Levy BD, Serhan CN, Van Dyke TE. RvE1 protects from local inflammation and osteoclast- mediated bone destruction in periodontitis. FASEB J 2006; 20: 401-3.

[96] Gao L, Faibish D, Fredman G, Herrera BS, Chiang N, Serhan CN, Van Dyke TE, Gyurko R. Resolvin E1 and chemokine-like receptor 1 mediate bone preservation. J Immunol 2013; 190: 689-94.

[97] Herrera BS, Ohira T, Gao L, Omori K, Yang R, Zhu M, Muscara MN, Serhan CN, Van Dyke TE, Gyurko R. An endogenous regulator of inflammation, resolvin E1, modulates osteoclast differentiation and bone resorption. Br J Pharmacol 2008; 155: 1214-23.

[98] Khaled M, Shibani NA, Labban N, Batarseh G, Song F, Ruby J, Windsor LJ. Effects of resolvin D1 on cell survival and cytokine expression of human gingival fibroblasts. J Periodontol 2013; 84: 1838-46.

[99] El-Sharkawy H, Aboelsaad N, Eliwa M, Darweesh M, Alshahat M, Kantarci A, Hasturk H, Van Dyke TE. Adjunctive treatment of chronic periodontitis with daily dietary supplementation with Omega-3 fatty acids and low-dose aspirin. J Periodontol 2010; 81: 1635-43.

[100] Wang CW, Colas RA, Dalli J, Arnardottir HH, Nguyen D, Hasturk H, Chiang N, Van Dyke TE, Serhan CN. Maresin 1 biosynthesis and proresolving anti-infective functions with human-localized aggressive periodontitis leukocytes. Infect Immun 2015; 14; 84: 658-65.

[101] Lopes F, Coelho FM, Costa VV, Vieira ÉL, Sousa LP, Silva TA, Vieira LQ, Teixeira MM, Pinho V. Resolution of neutrophilic inflammation by H2O2 in antigen-induced arthritis. Arthritis Rheum 2011; 63: 2651-60.

[102] Choe Y, Yu JY, Son YO, Park SM, Kim JG, Shi X, Lee JC. Continuously generated H2O2 stimulates the proliferation and osteoblastic differentiation of human periodontal ligament fibroblasts. J Cell Biochem 2012; 113: 1426-36.

[103] Lee YS, Bak EJ, Kim M, Park W, Seo JT, Yoo YJ. Induction of IL-8 in periodontal ligament cells by H2O2. J Microbiol 2008; 46: 579-84.
[104] Chan FK, Chun HJ, Zheng L, Siegel RM, Bui KL, Lenardo MJ. A domain in TNF receptors that mediates ligand-independent receptor assembly and signaling. Science 2000; 288: 2351-4.
[105] Deng GM, Zheng L, Chan FKM, Lenardo M. Amelioration of inflammatory arthritis by targeting the pre-ligand assembly domain of tumor necrosis factor receptors. Nat Med 2005; 11: 1066-72.
[106] Sousa LP, Alessandri AL, Pinho V, Teixeira MM. Pharmacological strategies to resolve acute inflammation. Curr Opin Pharmacol 2013; 13: 625-31.
[107] Lawrence T, Gilroy DW. Chronic inflammation: a failure of resolution? Int J Exp Pathol 2007; 88: 85-94.
[108] Garlet GP. Destructive and protective roles of cytokines in periodontitis: a re-appraisal from host defense and tissue destruction viewpoints. J Dent Res 2010; 89: 1349-63.