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The impact of the soluble epoxide hydrolase cascade on periodontal tissues

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Periodontitis is a chronic inflammatory disease with complex pathogenesis. Uncontrolled inflammation is driven by the immune system in response to accumulation of oral biofilm that leads to alveolar bone loss, bleeding, increased periodontal probing depth with loss of attachment of the connective tissues to the tooth, and ultimately, tooth loss. Soluble epoxide hydrolase (sEH) is an enzyme that converts epoxy fatty acids (EpFAs) produced by cytochrome P450 (CYP450) to an inactive diol. It has been shown that EpFAs display important features to counteract an exaggerated inflammatory process. Based upon this observation, inhibitors of sEH have been developed and are being proposed as a strategy to regulate proinflammatory lipid mediator production and the chronicity of inflammation. This mini review focuses on the impact of sEH inhibition on periodontal tissues focusing on the mechanisms involved. The interaction between Specialized Pro-Resolving Mediators and sEH inhibition emerges as a significant mechanism of action of sEH inhibitors that was not formerly appreciated and provides new insights into the role SPMs may play in prevention and treatment of periodontitis.

KEYWORDS

periodontitis, inflammation, lipid mediator, soluble epoxide hydrolase (sEH), soluble epoxide hydrolase (sEH) inhibitors

Introduction

Periodontitis is a chronic inflammatory disease with a complex pathogenesis that encompasses the host immune system and oral microbiome dysbiosis (1–3). The uncontrolled inflammation in the periodontium leads to the destruction of hard and soft tissues and, eventually, tooth loss (4). The unwanted excessive inflammatory reaction in periodontitis is due to the failure of endogenous inflammation resolution pathway activation (5). The cessation of the inflammatory process occurs when a balance between pro-inflammatory and pro-resolution mediators is achieved that determines health or disease (6, 7).

Inflammation is a natural and physiological reaction to injury or infection in all biological systems. This biochemical response is finely orchestrated and well-organized to fight pathogens and to restore homeostasis. It is generally accepted as a vital process for our existence. In an ideal scenario, an inflammatory reaction is self-limiting, characterized by a local increase of protein mediators (cytokines, chemokines) and lipid mediators (LMs) (e.g., prostaglandins and leukotrienes), vascular dilation and enhanced capillary permeability, and leukocyte trafficking and activation (8). The initiation or resolution of inflammation is dictated in large part by the metabolism of polyunsaturated fatty acids (PUFA) by cyclooxygenases (COX), lipoxygenases (LOX), or cytochrome P450 (CYP450) (9, 10).

Eicosanoids, a group of LMs, are oxidized derivates from the metabolism of arachidonic acid (ARA) by oxidative pathways, the COXs, LOXs, or CYP450 enzymes (8, 11). The resulting bioactive molecules, prostanoids, leukotrienes, hydroxyeicosatetraenoic acids (HETEs), epoxyeicosatrienoic acids (EETs), and hydroperoxyeicosatetraenoic acids (HPETEs) are largely

generated in inflammation, with distinct biological functions (12). Although much is known about the metabolism of polyunsaturated fatty acids by the cyclooxygenases and lipoxygenases enzymatic pathways and the activities of their downstream metabolites (13), the cytochrome P450 pathways are less understood, and are the center of this mini review. Notably, the EETs, as well as epoxides of other long-chain polyunsaturated fatty acids (EpFA) generated by the cytochrome P450 pathway, are important bioactive lipids with immunomodulatory actions in inflammation (14, 15). Most of these LMs are short-lived due to their rapid metabolization into inactive diols in the presence of soluble epoxide hydrolase (sEH), losing their ability to resolve inflammation (16). Worst, some of their diols contribute to inflammatory cytokine storm and block the initiation of the resolution phase (17). The sEH enzymes are largely found in the liver, brain, spleen, kidney, intestine, and joints (18–20), and high sEH expression was detected in chronic osteolytic inflammatory disorders, such as periodontitis and arthritis (19, 21–23).

Here, this mini review dissects the mechanisms uncovered to date explaining how sEH inhibition impacts the inflammatory process in periodontal tissues, protects against alveolar bone resorption, and speculates possible interactions/synergism between metabolites derived from sEH inhibition and the resolvent lipid mediators (lipoxins, resolvins) in periodontal tissues.

Periodontitis

Periodontitis is a chronic inflammatory and infectious disease culminating in a dysbiotic dental biofilm that disrupts the homeostasis of the subgingival environment (24). It is the sixth most prevalent disease among inflammatory osteolytic disorders worldwide, representing a significant public health problem (1, 2, 25). Clinically, periodontitis manifests as loss of clinical attachment, alveolar bone resorption, bleeding on probing, and periodontal pockets, and unlike gingivitis, these clinical symptoms are usually permanent. Individual periodontal susceptibility encompasses genetic, behavioral, and environmental factors that regulate the host immune response and generate ideal conditions for pathogenic biofilm microbial colonization (24, 26). Although microbial pathogens are associated with disease progression and severity, the molecular and biological basis of periodontitis is now realized to be the result of an excessive and uncontrolled inflammatory response rather than a classic infection with an exogenous organism(s) (7, 27). This shift in the periodontal disease paradigm began when increased levels of prostaglandin E_2 (PGE_2) were found in crevicular fluid of children and adults, and the levels of PGE_2 were correlated with disease severity. What caught the researcher's attention was that children had higher levels of PGE_2 than adults, and the capacity of PGE_2 to provoke periodontal tissue destruction (28–30). In this sense, the inflammation is an essential component of periodontal disease genesis; the tissues are destroyed by the host, not the bacteria.

As a chronic inflammatory disease, periodontitis stimulates a wide range of immune cells, from residents to infiltrating and patrolling cells, that disrupt tissue homeostasis and is characterized by a change in the immune cell composition (31). Additionally, the communication between the osseous and immune systems are intimately interconnected and responsible for bone destruction or remodeling (32–34). Alvarez and colleagues elegantly describe the spatiotemporal profile of the main gingival immune cell composition in ligature induced experimental periodontitis (35). Initially, neutrophils ($CD45^+LY6G^{high}LY6C^{mid}CD11b^{+/-}$) are the most abundant leukocyte cells in the gingiva, reaching their peak 24 h after ligature placement, indicating the activation of the innate immune response. This intense infiltration is accompanied by an over-expression of inflammatory cytokines (IL-1β, IL-6, IL-8, IL-12, and TNF-α), giving birth to a hyper-inflammatory phenomenon (36, 37). The transition from innate immunity to adaptive immune response begins on day 3 when tissue-resident macrophages are expanded, and circulating monocytes are recruited to be differentiated into M1-like macrophages ($CD45^+CD64^+CD11b^+MHCII^+$) (35). Macrophages are highly plastic cells that can exhibit dual roles in tissue repair or destruction, depending on their microenvironment (36, 38). Particularly, macrophage phenotypes, M1-like (pro-inflammatory subtype) or M2-like subsets (pro-resolving), are temporally associated with the different stages of experimental periodontitis progression (39). Although M1 macrophages are usually associated with an exacerbated inflammatory response, their presence and activation are needed to fight against pathogen invasion during the acute phase. They are implicated in producing several protein and lipid mediators (cytokines, chemokines, lipids mediators), which are fundamental to orchestrating the inflammatory response and guiding the return to tissue homeostasis, in a normal, self-limiting acute inflammatory response (40). On the other hand, resolving macrophages (M2-like) coordinate the resolution process of inflammation by removing dead cells through efferocytosis, producing anti-inflammatory cytokines (e.g., IL-10, IL-4, and TGF-β), counteracting osteoclast activity and boosting osteoblastic functions with augmented cystatin C (39, 40). Moreover, resolving macrophages are well-known synthesizers of Specialized Pro-resolving Mediators (SPMs), a fundamental lipid mediator class switching that defines inflammation termination and resolution stimulation (9, 41).

Failure of the acute response to resolve normally leads to chronicity and chronic inflammatory diseases which include periodontal disease. In experimental periodontitis, T cells ($CD45^+CD3^+$) represent roughly 70% of all cell populations in the gingiva, reaching the peak at day 10 post-ligature (35). Specifically, alveolar bone resorption relies on the imbalance between T-helper type 17 and regulatory T cells (Treg) (40, 42). Although Th17 cells have a physiological immune-protective role in the oral mucosa, their exaggerated activation establishes an interaction with the osteoclast by directly inducing RANKL expression by osteoblasts and periodontal ligament fibroblasts through IL-17A and IL-17F synthesis, ultimately leading to bone loss (34). The $CD4^+$ Th17 cells were first described in the early 2000s (43–45). This abnormal reaction is associated with augmented IL-23 levels, from the IL-12 cytokine family (46). Further, transforming growth factor-beta (TGF-beta) primes IL-23R, enhancing the Th17 responsiveness to IL-23 (45), culminating in intense neutrophil transmigration to inflamed sites and RANK/RANKL axis incitement (47). To the contrary, another subset of T cells, Tregs, are regulators of exaggerated inflammatory reactions, maintaining humoral tolerance and reestablishing homeostasis (48). The mainly immunosuppressive Treg

features are linked with the release of inhibitory cytokines, such as IL-10, TGF-beta (48), and IL-35 (49), and by dampening dendritic cells *via* the interaction between cytotoxic T-lymphocyte antigen 4 (CTLA4) and cluster of differentiation (CD) 80/86 (48). Curiously, in experimental periodontitis, Tregs from cervical lymph nodes lose their capacity to counteract osteoclastogenic activity, presenting lower expression of Foxp3, and show a Th17-type response (increased IL-17 gene expression) without fully transdifferentiating into Th17-like cells (50).

Endorsing the immunological aspects of periodontal disease progression, inflammatory lipid mediators are dramatically elevated in periodontal tissues and crevicular fluid, such as leukotriene B_4 (LTB_4) and prostaglandin E_2 (PGE_2) (28–30). Apart from inflammatory lipid mediators, differences in the Specialized Pro-Resolving Mediators (SPMs) and other lipid mediator profiles are associated with the stages of periodontal inflammation (51, 52). Gingival samples from healthy and periodontitis subjects showed distinct lipid profiles in PCA (Principal Component Analysis) of metabolipidomics (51). Notably, none of the SPMs were found to be higher in periodontitis than in healthy subjects, although several pathway markers for omega-6 driven SPMs (e.g., 5-HETE and 15-HETE), D-series resolvins (e.g., 4-HDHA and 7-HDHA), and E-series resolvins [15(S)-HEPE] were higher in periodontitis. Moreover, the resolvin E1 receptor (BLT1) was lower in periodontitis than in healthy subjects' samples (51). These findings suggest that in periodontitis, there is an effort by the body to re-establish homeostasis and initiate the resolution process through SPM synthesis; however, even though essential pathways seem to be activated, none of the final SPM metabolites were found at physiological levels, enough to exert cell function, and SPM receptor expression was decreased.

Soluble epoxy hydrolase and its inhibition

John Casida's group led the discovery of soluble epoxide hydrolase in the 1970s, when they described an unknown epoxide hydrolase activity in the soluble fraction of liver homogenates (53–55). Interestingly, the fundamental biological role of sEH is proved by its conservation among species, from chordates to mammalians (56), and it is mostly expressed in the liver, kidney, intestine, brain, and endothelial cells (57).

Soluble epoxide hydrolase was found to be essential for the hydrolysis of the epoxy fatty acids. The epoxy fatty acids are generated by polyunsaturated fatty acid metabolism [including ARA, linoleic acid (LA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA)] through the enzymatic activity of cytochrome P450, resulting in lipid mediators with a broad spectrum of biological functions at the systemic and cellular levels (58). The epoxidized metabolites are primarily anti-inflammatory and resolution lipid mediators, such as epoxyeicosatrienoic acids (EETs) from omega-6 ARA, epoxyeicosatrienoic acids (EEQs) from omega-3 EPA, and epoxydocosapentaenoic acids (EDPs) from omega-3 DHA (Wagner et al., 2017). However, in the presence of sEH (their principal regulatory enzyme), these epoxy metabolites are rapidly transformed into inactive diols, which could also possess pro-inflammatory functions (59).

In this regard, targeted inhibition of sEH during the inflammatory process, and consequently, enhancement of epoxy fatty acid bioavailability, offers an attractive strategy for inflammation control. The first inhibitors designed were too unstable for *in vivo* experiments (60). With the advent of crystallographic studies and the discovery of dicyclohexyl urea as a reversible inhibitor of soluble epoxide hydrolase (61), the next generation of inhibitors was produced with higher efficacy, stability, pharmacokinetics, and minor off-target activity (62). Since then, many studies have been carried out in several inflammatory models with promising results. Below, we summarize the findings on soluble epoxide hydrolase inhibition in periodontal tissues.

Inhibition of soluble epoxy hydrolase in periodontal tissues and *in vitro* assays

The pharmacological inhibition of soluble epoxide hydrolase and its impact on inflammatory, autoimmune, and pain disorders has been widely explored (63–66). Nevertheless, its application in periodontitis or other orofacial conditions is new (18, 21–23, 67). There are only a few studies involving the inhibition of the soluble epoxide hydrolase enzyme in periodontal disease (21–23); therefore, we will address them in detail. Still, in our bibliographic search, we found only one article that shows the impact of EETs on osteoclasts (68) and another on fibroblasts (69), although both are not focused on oral tissues.

Trindade-da-Silva and colleagues initially demonstrated the protective effect of soluble epoxide hydrolase inhibitors (TPPU) on alveolar bone resorption in experimental periodontitis induced by *Aggregatibacter actinomycetemcomitans* (*Aa*), as exemplified in **Figure 1** in a ligature-induced periodontitis model (21). The potential bacteriostatic effect of the sEH inhibitor was discarded when no changes in *Aa*' growth were found in the presence of TPPU. Subsequently, by measuring the distance between the cemento–enamel junction and the alveolar bone crest, the researchers showed that by inhibiting soluble epoxide hydrolase, lower bone loss in infected animals was detected, altering the phenotype of experimental periodontitis. Interestingly, treatment with EETs, one of the CYP450 metabolite branches that is inactivated by sEH, did not prevent bone loss. Additionally, the treatment with sEH and EETs concomitantly, did not result in a greater prevention of bone loss. Corroborating evidence was provided by genetic inhibition of soluble epoxide hydrolase by gene KO, which showed reduced bone loss, recapitulating the previous observations from the pharmacological inhibition by TPPU (21). Mechanistically, pharmacological inhibition and genetic ablation decreased activation of the RANK/RANKL/OPG axis in gingival tissue. In agreement, the reduced protein expression of MCP-1 (monocyte chemotactic protein 1), a vital monocyte recruiter associated with lower levels of F4/80 (EGF-like module-containing mucin-like hormone receptor-like 1) in the gingiva, endorses that the protective effect of sEH inhibition is related to the regulation of the exaggerated inflammation and the immune system response (21). The decreased inflammatory process was tracked by two essential downstream stress kinases, mitogen-activated protein kinase phosphorylation (p38 and JNK 1/2), which ultimately led to nuclear factor kappa B (NFκB) activation (70). Animals treated with TPPU, TPPU and EETs, or in sEH KOs,

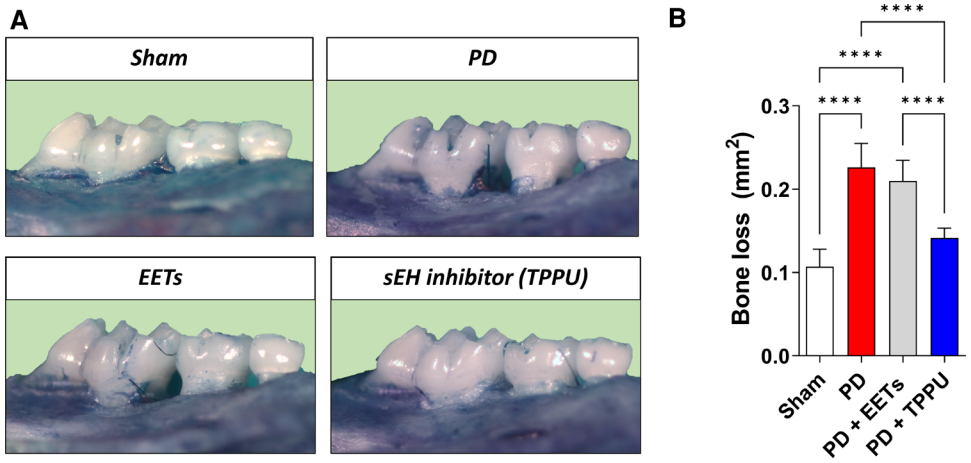

FIGURE 1
Inhibition of soluble epoxide hydrolase prevents alveolar bone loss in experimental periodontitis in mice. (A) Representative images from a palatal view of maxillary molars. TPPU was used as the soluble epoxide hydrolase inhibitor. (B) Bone loss was quantified as the area between the cementum-enamel junction and the alveolar bone. PD, periodontal disease; EETs, epoxyeicosatrienoic acids. ****$P < 0.0001$. The data are expressed as mean ± S.D; $n = 5$ animals per group.

showed greatly reduced phosphorylation of p38 and JNK 1/2. Finally, pharmacological sEH inhibition and knockout animals (sEH$^{-/-}$) showed inhibition of phosphorylation of the ER stress sensor (PERK, protein kinase RNA-like ER kinase); eIF2α, eukaryotic initiation factor 2α; IRE1, inositol-requiring enzyme 1; sXBP1, spliced X-box binding protein 1 and associated apoptosis (c-Caspase-3 and immunoglobulin binding protein) (21).

Napimoga and collaborators, in a succeeding study by the same research group, showed that inflamed gingival tissue induced by experimental periodontitis expressed higher levels of sEH than control animals. Pharmacological inhibition of sEH dampened this expression, and correlated with lessening disease severity (22). Using an RNA array to explore the innate and adaptive immune systems, sEH inhibition diminished the expression of toll-like receptors 1 and 9 (Trl1 and Trl9), which play a crucial role in inflammatory cytokine release upon triacylated lipopeptide recognition (71) and activation of osteoclastic functions (72). T cells were also affected. The expression of Cd8 and Cd4 was diminished, as well as Cd40l, interferon-alpha2 (Ifnα2), and interferon-beta (Ifnβ) (21). Downregulation of Cd40l impairs B-cell activation and, therefore, the production of IL-2, IL-6, and TNF-alpha (73). The signal transducer and activator of transcription 4 (Stat4) is a factor that contributes to IL-12, IL-23, and IFN-1 production, in addition to differentiating Th1 and Th17 cells (74), which was also reduced by sEH inhibition. These findings reinforce the concept that by inhibiting sEH, the unwanted lymphocyte response is managed, as also demonstrated in a collagen-induced model of arthritis (19), preventing osteoclastogenic activity in the periodontium (21) and knee joint (19).

Recently, Abdalla and coworkers thoroughly characterized the impact of the sEH/EET axis on gingival macrophage plasticity in experimental periodontitis in mice. The work revealed for the first time that pharmacological inhibition of sEH fosters communication between epoxy fatty acid metabolites, increasing the levels of Specialized Pro-Resolving Mediators [e.g., resolvin (Rv) E-series and lipoxins] in saliva, as well as their respective receptors in the gingival tissues (23).

Mechanistically, pharmacological sEH inhibition suppressed alveolar bone loss *via* actions on inflammatory osteolytic factors, such as Il17a and RANKL. In metabolipidomic analyses, soluble epoxide hydrolase inhibitor treated animals showed lipid profiles that were distinct from experimental periodontitis and control animals in two-dimensional and three-dimensional Principal Component Analyses. The foremost lipid mediators enhanced by sEH inhibition were RvE1, RvE2, and LXA_4, well-known SPMs with robust immunoresolvent features that guide healing. Moreover, 20-hydroxy LTB_4 was enhanced, inferring an inactivation of LTB_4, a critical inflammatory lipid mediator. Further, the Specialized Pro-Resolving Mediator receptors (LTB4R1, CMKLR1/ChemR23, and ALX/FPR2) were also found to increase in gingival tissue, suggesting greater effectiveness of SPM activity at the site of inflammation. In macrophages, the pharmacological inhibition of soluble epoxide hydrolase stimulated a dynamic transcriptional reprogramming of inflammatory macrophages toward resolving macrophages (characterized by CD11c$^+$/CD206$^+$ double-positive cells in the CD45$^+$/CD11b$^+$/CD64$^+$ macrophage population), associated with reduced expression of Il1β, TNFα, Il12, and Nos2. Finally, *in vitro* assays revealed that sEH inhibition and EET treatment triggered SPM release in bone marrow derived macrophages (BMDMs) in both inflammatory and resolvent macrophages (23). These findings are summarized in **Figure 2**.

The direct influence of the EETs/sEH/DHET axis on osteoclast differentiation and activity was explored *in vitro* using BMMCs (Bone marrow mononuclear cells) and RAW264.7 murine cells (68). Authors showed that DHETs, the inactive diol form of EETs, could not reduce TRAP-positive cells, but increased their number. Differently, treatment with EETs or sEH inhibitors (TPPU) significantly diminished the number of multinucleated TRAP-positive cells. Likewise, bone resorption pits were hardly impaired by EETs and sEH inhibition, as well as expression of RANK, TRAP, cathepsin K (CK), and matrix metalloproteinase (MMP)-9. Further, in an osteoblast precursor cell line (MC3T3), EETs reduced the ratio between RANKL:OPG (68). In TGF-β1-induced activation of murine

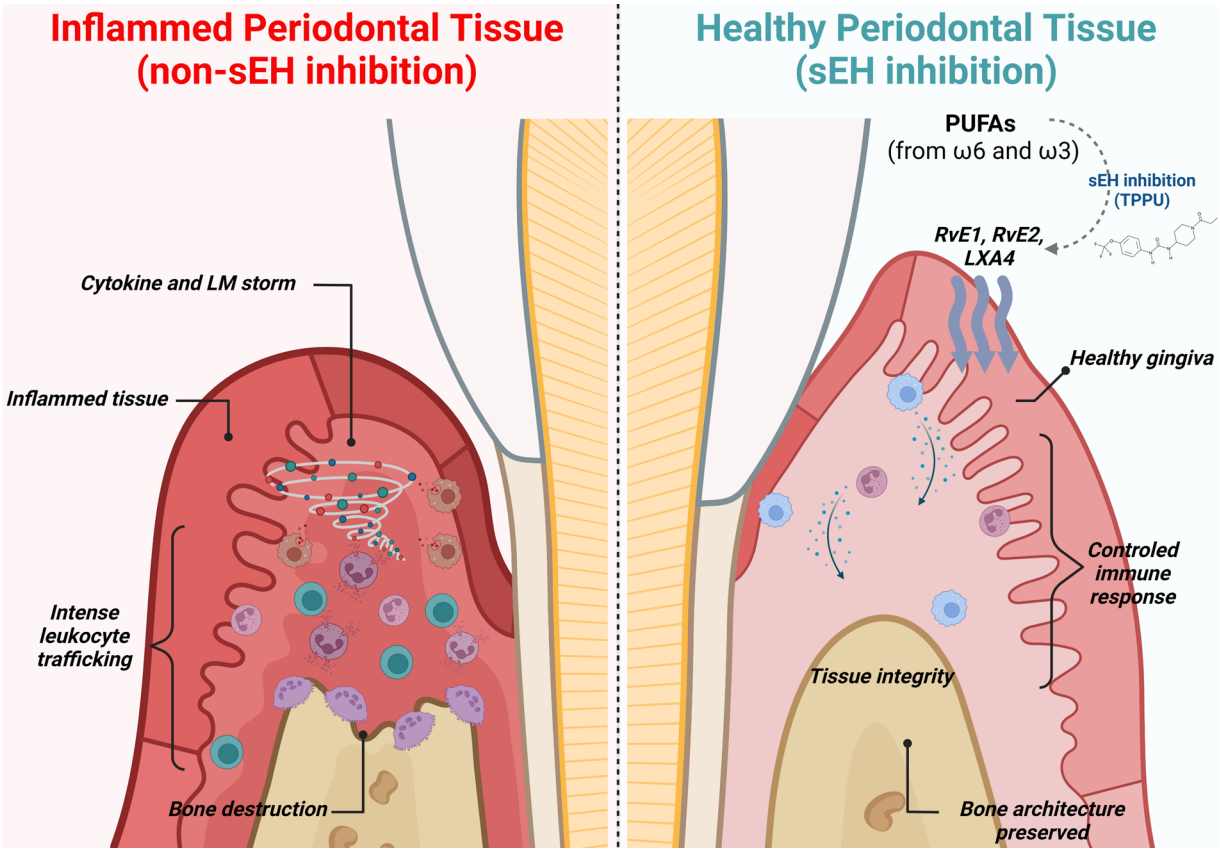

FIGURE 2
Immune modulation and lipid mediator synthesis induced by sEH inhibition in experimental periodontitis. During periodontitis, the immune system drives an unwanted and uncontrolled inflammatory reaction, leading to an intense release of inflammatory cytokines, chemokines, and lipid mediators, ultimately leading to alveolar bone loss, gingival tissue damage, and increased probing depth (left panel). Pharmacological inhibition of sEH improves the bioavailability of epoxy fatty acids (EpFAs), shifting polyunsaturated fatty acid (PUFA) metabolism and favoring production of Specialized Pro-Resolving Mediators. Further, macrophages undergo phenotypic reprogramming towards resolving and repairing features associated with releasing anti-inflammatory cytokines. Innate immunity is controlled and well-orchestrated. Finally, inhibition of sEH prevents osteoclastic activation, preventing alveolar bone loss.

fibroblasts (NIH3T3), EETs attenuate cell activation by impairing the expression of collagen, smooth muscle alpha-actin (α-SMA), and proliferating cell nuclear antigen (PCNA) in a peroxisome proliferation activated receptor γ (PPARγ) dependent-manner (69).

Conclusions and perspective

The pharmacological inhibition of sEH has shown impressive results in inflammatory diseases and has been the subject of extensive research. Concerning the dental medicine area, including painful orofacial conditions and periodontal disease, a few studies have been conducted, revealing promising findings. As a note, sEH inhibitors are in the clinical development phase, making them a promising forthcoming therapeutic strategy. Nevertheless, a profound molecular mechanistic analysis of how sEH inhibition acts through the immune system must be carried out. Future research should deeply analyze the impact of sEH inhibition on immune system cells and how they respond in its absence. Nevertheless, recent findings demonstrate that the inhibition of sEH influences the production of SPMs (omega-3 and -6 fatty acids metabolites from CYP450), which paves the way for a new perspective on its mechanism of action, as well as pharmacological implications, as they boost resolution pathways of inflammation rather than silencing them.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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