

SPECIAL ISSUE: Oral Regional Immune Mechanisms and Systemic Homeostasis

TREM-1: a pathogenic hub mediating the link between oral inflammation and systemic diseases

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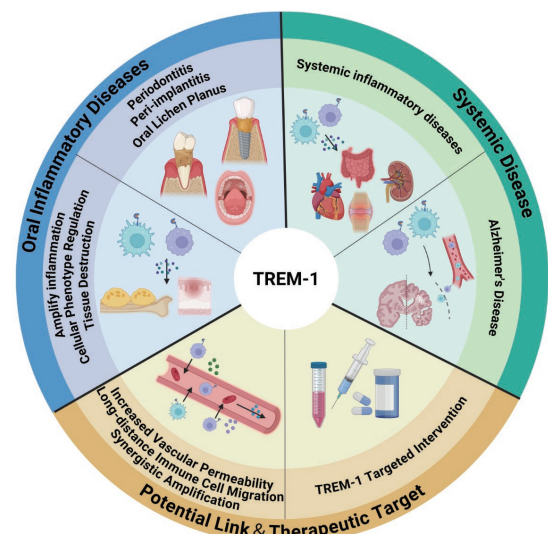
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ABSTRACT: Triggering receptor expressed on myeloid cells 1 (TREM-1) is a critical amplifier of innate immune responses, orchestrating pathophysiology across diverse inflammatory conditions. In the oral cavity, TREM-1 activation promotes the development of periodontitis, peri-implantitis, and oral lichen planus by polarizing myeloid cells toward a pro-inflammatory state, enhancing pro-inflammatory cytokine release, and accelerating tissue degradation and bone resorption. Notably, this TREM-1-driven myeloid dysregulation also underpins severe systemic comorbidities, including atherosclerotic cardiovascular disease (ASCVD), diabetic kidney disease (DKD), and Alzheimer's disease (AD). This review synthesizes current knowledge to delineate the TREM-1 axis as a pathogenic hub in oral-systemic crosstalk, specifying three dissemination routes: systemic leakage of local mediators after barrier disruption, peripheral migration of epigenetically primed TREM-1⁺ cells, and synergy with metabolic risks. We further highlight soluble TREM-1 (sTREM-1) as a promising biomarker reflecting cumulative inflammatory burden. Ultimately, combining established oral therapies with emerging TREM-1-targeted strategies offers a mechanistically grounded framework to disrupt the oral-systemic disease continuum, providing novel therapeutic avenues for inflammatory comorbidities.

KEYWORDS: TREM-1 signaling pathway, inflammation, oral-systemic axis, therapeutic target



1 Introduction

Triggering receptor expressed on myeloid cells 1 (TREM-1), a transmembrane glycoprotein belonging to the immunoglobulin superfamily, is expressed on the surface of neutrophils, monocytes, and macrophages and regulates myeloid cell inflammation. TREM-1, once up-regulated, collaborates with other Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), to amplify the inflammatory pathway^[1], which leads to massive release of proinflammatory cytokines and chemokines, thus triggering a cascade amplification of inflammation^[2].

In recent years, knowledge about TREM-1 has evolved from considering this molecule as an inflammatory receptor in myeloid cells to viewing TREM-1 as a potential hub linking local

immunopathology with systemic pathophysiological changes^[3]. Given the unique characteristics of oral medicine, TREM-1 may mediate the systemic spread of oral-derived inflammation to distant organs and tissues, a concept that aligns with the emerging framework of homeostatic medicine, which views disease as a failure of systemic self-regulation^[4,5]. However, the molecular mechanism behind such pathological process is still unknown. Key unresolved questions include how TREM-1 is activated in the oral inflammatory microenvironment, how these inflammatory signals cross local tissue barriers to impact distant extraoral organs, and whether TREM-1 exhibits consistent biological functions in both the oral cavity and systemic circulation.

In order to address these major issues for science, we summarize all the information on TREM-1 activation pathways and their consequences in local oral pathology herein. Furthermore, we analyze its molecular characteristics and signaling regulatory mechanisms, and elucidate the shared regulatory pathways between TREM-1 and systemic diseases, including cardiovascular disease, DKD, inflammatory bowel disease (IBD), and sepsis. TREM-1 is an

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important mediator in the innate immune response by amplifying the inflammation signal via cascading events and plays a common pathophysiological bridge among sepsis, chronic inflammation; autoimmune diseases; neurodegeneration; and other systemic disorders.

Additionally, soluble TREM-1 (sTREM-1) is a well-established biomarker of inflammatory burden in both oral and systemic diseases^[6]. In addition to these studies, we here discuss potential uses as well as limitations of TREM-1 inhibition or stimulation for both local and systemic pathologies: with a view toward providing novel mechanistic insights into cross-talk between periodontitis and other diseases, which can serve as basis for multidisciplinary research in this field.

2 Molecular biology and signaling regulation of TREM-1

2.1 Gene and structure

As a type I transmembrane protein, TREM-1 is encoded by the *Trem1*, which maps to human chromosome 6p21.1. Composed of 234 amino acids, the mature TREM-1 comprises a single extracellular V-type immunoglobulin-like domain, a transmembrane region, and a short cytoplasmic tail. Notably, its short cytoplasmic C-terminal tail lacks a signaling sequence; thus, TREM-1 activity depends primarily on electrostatic interactions between positively charged lysine residues in its transmembrane domain (TMD) and negatively charged aspartic acid residues in the TMD of the adaptor protein DNAX-activating protein of 12 kDa (DAP12)^[7]. This association generates the active TREM-1/DAP12 receptor that transduces signals inside cells.

2.2 TREM-1 signal transduction

As a surface receptor on myeloid cells, TREM-1 is activated by binding to specific ligands. These ligands consist of pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and potential endogenous ligands^[2]. This dual function of recognizing both endogenous danger signals and exogenous pathogens enables TREM-1 to act as a key link connecting aseptic inflammation and infectious inflammatory responses, thus^[8]. So far, the experimentally validated ligands of TREM-1 have expanded from the classic HMGB1 and Hsp70 to five confirmed molecules^[3,9], with the addition of extracellular cold-inducible RNA-binding protein (eCIRP) and peptidoglycan recognition protein 1 (PGLYRP1)^[10,11]. These ligands enhance and sustain myeloid cell inflammatory responses by either directly binding to TREM-1's extracellular immunoglobulin-like domain or indirectly interacting with other components of the receptor complex^[2,4]. Computational simulations of TREM-1 with its five known ligands revealed that the complementarity determining regions (CDRs), particularly the CDR3 loop, are the principal domains mediating ligand recognition by TREM-1. Hotspot residues on the IgV-like domain of TREM-1 play a critical role in binding to multiple ligands^[12]. TREM-1 binding to its ligand induces phosphorylation of tyrosine residues within the immunoreceptor tyrosine-based activation motif (ITAM) on the cytoplasmic domain of DAP12, a process that is primarily regulated through Src family tyrosine kinases^[13].

The phosphorylated ITAM recruits and activates the spleen tyrosine kinase (Syk) and Zeta-chain-associated protein kinase 70

(ZAP70)^[14], which in turn activates several downstream signaling pathways, including the Phosphatidylinositol 3-kinase (PI3K)-Protein Kinase B (AKT) signaling pathway, the Phospholipase C gamma 2 (PLCγ2)-Ca²⁺-Nuclear factor kappa B (NF-κB) pathway, and actin cytoskeletal rearrangement via the Vav family. This finally drives the secretion of inflammatory cytokines, cell survival signals, and a metabolic reprogramming, which allows TREM-1 to play its critical signal transducing function as an amplifier of the inflammatory cascade^[13].

There is tight cooperation between TREM-1 and TLR4 signaling. Unlike the conventional "single receptor-single ligand" framework, TREM-1 mainly enhances the TLR4 pathway through physical co-localization at the membrane level and cross-integration of intracellular signaling networks. Various studies show that TREM-1 and TLR4 gather together and co-localize on myeloid cell membranes, potentially forming multi-receptor signaling platforms^[15]. At the cellular signal transduction level, the TREM-1 signaling pathway overlaps with the TLR4-Myeloid differentiation primary response 88 (MyD88)-dependent pathway at many nodes. They jointly regulate neutrophil oxidative burst and amplify inflammatory responses^[16]. Furthermore, TREM-1 signaling strongly enhances TLR4-mediated NF-κB activation to facilitate transcriptional induction of proinflammatory cytokines like interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α), as well as chemokines^[1,17]. Silencing TREM-1 can markedly reduce the expression of key molecules in the TLR4 pathway. These molecules include adaptors such as MyD88 and CD14, as well as downstream inflammatory factors like IL-1β, MCP-1 and IL-10. This finding proves that TREM-1 cooperates with TLR4 to strengthen the inflammatory reaction of macrophages stimulated by LPS. On the other hand, TLR4 stimulation also induces more TREM-1, which in turn promotes even more TLR4, inducing thus an auto-amplifying cycle; blocking of TREM-1 signaling significantly inhibits TLR4-mediated cytokine synthesis, which supports a role for it as an "amplifier" of the TLR4-dependent inflammatory response^[18].

2.3 Negative feedback mechanisms

To prevent excessive inflammation and tissue damage, the host has evolved multiple negative feedback mechanisms that tightly control TREM-1 expression and signaling. First, TREM-1 exists in two forms: membrane-bound (mTREM-1) and soluble (sTREM-1). There are two main ways to produce sTREM-1: first, matrix metalloproteinases (especially MMP-9) enzymatically cleave and shed the extracellular domain of membrane-bound TREM-1^[19], alternative splicing of TREM1 mRNA directly translates into a soluble form that lacks the transmembrane domain^[20]. sTREM1 keeps the ability to bind ligands but cannot start intracellular signaling; instead, it binds ligands competitively to inhibit membrane TREM-1 signaling. Thus, it acts as a decoy receptor that competitively blocks membrane TREM-1 activation, providing negative feedback regulation under normal physiological conditions^[21]. Second, the adaptor molecule DAP12 itself possesses bidirectional regulatory capacity, and. Repression of the TLR downstream Extracellular Signal-Regulated Kinase (ERK) cascade is achieved through recruitment of molecules such as Docking protein 3 (DOK3), thus indirectly limiting the proinflammatory action of TREM-1. At the level of transcription, and under certain conditions, at a later stage of an inflammatory process or depending on particular microenvironments, nuclear receptors e.g., Retinoid X

Receptor (RXR), Liver X Receptor (LXR), which have the potential for down-regulating TREM-1 expression in order to avoid over-inflammation damage. Furthermore, some of the endogenous molecules, like Extracellular cold-inducible RNA-binding protein (eCIRP), might also play a role, but how is yet to be determined^[13]. The interplay of all these positive and negative feedback loops finally defines the ultimate function of TREM-1 during an immune response, as a regulator of protective host defence only or of detrimental pathological injury.

2.4 Clinical significance of sTREM-1

As discussed above, sTREM-1 production per se represents an important negative feedback loop in humans, and, even more importantly, as it does not degrade and readily measures in body fluids such as blood (serum) or other secretions (saliva, urine), levels of soluble TREM-1 are an indirect measure of membrane-bound TREM-1 activity and the total burden of inflammation^[22]. sTREM-1 has emerged as a potential marker of inflammation^[23].

During infection/inflammation, sTREM-1 increases significantly in parallel to the severity of the disease^[24]; therefore, it can be used as an easy-to-use marker monitoring local and systemic inflammatory activity, and also for monitoring therapeutic response. sTREM-1 in saliva can serve as an auxiliary diagnostic biomarker to distinguish periodontitis from gingivitis and healthy periodontal status, and exhibits potential value in predicting treatment response at the early stage of treatment^[25]. Elevated levels of sTREM-1 in patients with sepsis are closely associated with an increased risk of death^[6]. And the levels of sTREM-1 can also act as prognostic indicators of sepsis severity^[26]. At the same time, sTREM-1 levels are positively correlated with the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, making it a prognostic marker that reflects the severity of sepsis^[26]. In bronchoalveolar lavage fluid (BALF), sTREM-1 shows high sensitivity and specificity for the diagnosis of bacterial pneumonia, and the sTREM-1/C-reactive protein (CRP) ratio enables early diagnosis of ventilator-associated pneumonia (VAP)^[27]. Studies have identified sTREM-1 as a potential biomarker for predicting long-term functional recovery in patients with acute ischemic stroke. Higher circulating sTREM-1 concentrations are associated with more severe impairments three months after onset, assessed using the modified Rankin Scale (mRS)^[28]. In conclusion, sTREM-1 is not just an endogenous negative feedback-regulated molecule in the TREM-1 cascade; it can be used clinically to indicate the excessive activation of TREM-1 or inflammation. It boasts considerable translational application value in the management of both oral localized and systemic inflammatory diseases.

3 Activation and pathogenic role of TREM-1 in oral inflammation

3.1 Pro-inflammatory role of TREM-1 in oral infectious diseases

3.1.1 Periodontitis

Many investigations have revealed that the TREM-1 signal is a crucial player during the progression of periodontitis. Firstly, clinical samples have confirmed a close correlation between TREM-1 expression and periodontitis. The salivary TREM-1 level in

patients with periodontitis is higher than that in patients with gingivitis and healthy individuals. The AUC value of TREM-1 for distinguishing periodontitis from the healthy status is no less than 0.9, with the sensitivity ranging from 82.1% to 92.8% and the specificity ranging from 83.3% to 88.9%. TREM-1 expression was significantly higher in the periodontitis group compared to the healthy control group, and it showed strong positive associations with clinical measures such as plaque index, probing depth, attachment loss, and probing bleeding positivity rate^[24,29].

Secondly, various pathogenic factors in the periodontitis microenvironment can act as upstream signals to activate the pro-inflammatory pathway of TREM-1 through transcriptional upregulation and synergistic activation. The initial trigger in periodontitis is pathogenic bacteria present in a dental plaque biofilm, with *Porphyromonas gingivalis* being the most commonly accepted principal pathogen to induce TREM-1 expression. In fact, the broad regulatory role of the oral microbiota in host immunity and epithelial barrier function has been established as a core mechanism in the pathogenesis of oral mucosal diseases^[30]. Thus, the activation of TREM-1 by oral microbes represents a key inflammatory amplification node within the microbe-host interaction axis. An in vitro study demonstrated that *P. gingivalis* significantly up-regulates TREM-1 mRNA and protein expression on the surface of the MM6 monocytic cell line and human primary neutrophils^[23]. Other periodontal pathogens are also considered capable of stimulating TREM-1 expression, and this expression is positively linked to TREM-1 levels in tissues^[31]. At the mechanistic level, TREM-1 is considered an important mediator of the polarization process by studies using Trem1 gene knockout mice and cell cultures. TREM-1 expression was found in gingival tissue samples derived from individuals with periodontitis. TREM-1 is significantly increased and positively correlated to gene expression of M1 marker genes. The studies on its mechanism show that TREM-1 promotes polarization of macrophages toward the inflammatory M1 type via the Signal transducer and activator of transcription 3 (STAT3)/hypoxia-inducible factor 1 α (HIF-1 α) signal transduction pathway, while also inhibiting M2 phenotype development. In Trem1^{-/-} mice with periodontitis, the amount of macrophages infiltrated into the lesion site decreased, and M1 marker expression decreased with a significant reduction in alveolar bone resorption^[32]. Taken together, these findings demonstrate that TREM-1 does more than enhance inflammation. It alters macrophage polarization as well: promoting the recruitment of immune cells with possible tissue repair capacity towards a chronic pro-inflammatory pathologic condition.

In addition to regulating macrophage polarization, TREM-1 also accelerates the progression of periodontitis by promoting the release of inflammatory factors. TREM-1 expression is significantly increased following stimulation with *P. Gingivalis*, and it can promote the release of various pro-inflammatory mediators, including IL-1 β , interleukin-6 (IL-6) and IL-8^[33]. These cytokines play distinct yet complementary roles in the development of periodontitis: IL-1 β and TNF- α directly start osteoclast differentiation and bone resorption by increasing Receptor activator of nuclear factor- κ B ligand (RANKL) expression; IL-6 indirectly enhances Interleukin-17A (IL-17A)-mediated bone damage by promoting T helper 17 (Th17) cell differentiation^[34]; as a key chemokine, IL-8 continuously draws in neutrophil infiltration, forming a self-sustaining positive feedback loop of inflammation^[35].

As Figure 1 illustrates, the molecular pathways underlying

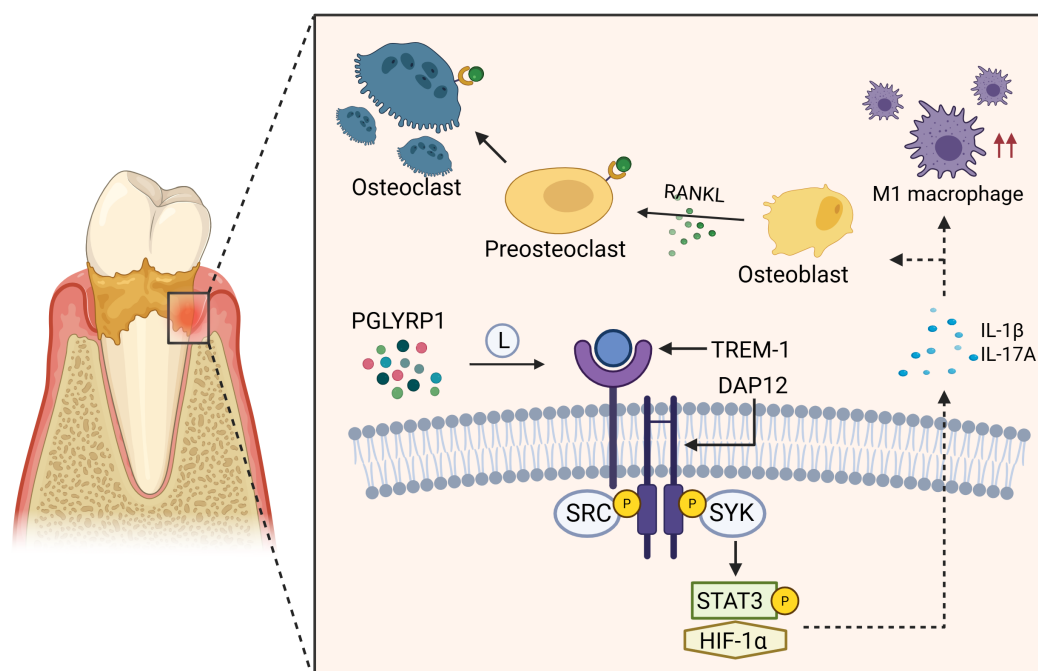


Figure 1 TREM-1-mediated inflammatory amplification in periodontitis. Periodontitis pathogens upregulate TREM-1 expression on myeloid cell surfaces. PGLYRP1, acting as a TREM-1 ligand, binds and activates the TREM-1/DAP12 signaling complex, thereby amplifying the inflammatory response. In this way, through the STAT3/HIF-1 α pathway, it drives M1 macrophage polarization and robustly releases pro-inflammatory cytokines, including IL-1 β , TNF- α , and IL-6. It activates osteoclasts by modulating the RANKL/OPG balance. Finally, the mechanism promotes alveolar bone resorption, thus driving the progression of periodontal disease. PGLYRP1, peptidoglycan recognition protein 1.

TREM-1-mediated alveolar bone resorption in periodontitis. With an animal model of periodontitis, there is a direct link between TREM-1 and destruction of bones: treatment with the anti-TREM-1 peptide LP17 locally reduced alveolar bone loss by decreasing IL-17A levels and changing the RANKL/Osteoprotegerin (OPG) balance. The RANKL/OPG ratio represents the core axis of regulation driving osteoclast formation and resorptive activity by amplifying upstream inflammatory signals (IL-1 β , TNF- α , IL-17A), TREM-1 indirectly enhances osteoclast activity, leading to alveolar bone resorption eventually^[36]. This provides critical evidence that TREM-1 is an attractive target for therapy against periodontitis.

The integrity of the interface between hard and soft periodontal tissues relies on the ordered structure of collagen fibers in the periodontal ligament^[37]. TREM-1 activation also triggers the release of MMPs, which disrupt the collagen fiber structure of the periodontal ligament. After macrophages were stimulated by *Fusobacterium nucleatum*, TREM-1 activation was accompanied by a notable rise in MMP-3 and MMP-9 secretion^[38]. Therefore, TREM-1 acts not only as an inflammatory amplifier, but also as a key driver for structural destruction at the interface between periodontal hard and soft tissues^[37]. More importantly, the inflammatory microenvironment resulting from sustained TREM-1 activation may interfere with the osmotic equilibrium and electroneutrality conditions required for intrafibrillar collagen mineralisation, thereby compromising functional regeneration^[39].

3.1.2 Peri-implantitis

Periodontitis and peri-implantitis both result from a microbial dysbiosis which eventually leads to destruction of periodontal supporting tissue; they have very similar characteristics with regard to the pathogens present, inflammatory signal pathways, and the

way bone destruction happens. These similarities make them a perfect comparison model to verify if the mode of action of TREM-1 can be transferred from one disease to the other.

The TREM-1/PGLYRP1/MMP-8 axis was systematically and thoroughly examined regarding its expression pattern during peri-implantitis by researchers, from which altogether 77 patients were enrolled and concentrations of sTREM-1, PGLYRP1, MMP-8 as well as Tissue inhibitor of metalloproteinase 1 (TIMP-1) from their salivary samples were quantified by the authors^[40]. The results of this study indicated that there was not any significant difference between the levels of these four indicators in the patients who had peri-implantitis and periodontitis. This finding indicates that the TREM-1 axis is also involved in inflammation of peri-implantitis, and suggests that the significance of sTREM-1 as an inflammatory marker does not depend on the anatomical differences existing between natural teeth and dental implants.

Furthermore, we also provide some useful evidence on how the TREM-1 axis could be involved in two key steps of peri-implantitis onset and development: first, PGLYRP1 is a ligand to TREM-1 and an increase in its level indicates both greater PAMP burden from the mouth flora and greater upstream inducers leading to upregulation of the TREM-1 receptor.

Second, MMP-8 plays an important role as an effector molecule for collagen degradation and high expression levels of MMP-8 indicate that the step of extracellular matrix breakdown has been activated^[29,40].

3.2 Pro-inflammatory role of TREM-1 in oral non-infectious disease: oral lichen planus

Oral lichen planus (OLP) represents a T cell-mediated chronic inflammatory disease whose worldwide prevalence varies between

0.5-3%, while its malignant potential ranges from 0.8-1.5%^[41]. In contrast to periodontitis, which is produced by pathogens, autoimmunity plays a major role in the etiopathogenesis of OLP. Its clinical presentations are varied and tend to recur, which has a considerable impact on the quality of life of affected patients^[42]. This condition offers an important research opportunity to assess the function of TREM-1 in non-infectious, immune-mediated oral inflammation. Shang and his colleagues used single-cell RNA sequencing technology to analyze oral mucosal tissue, which provided key proof of TREM-1's central role in this disease. Amongst the differential enrichment of major cell types in inflamed oral mucosal tissue was myeloid cells, which constitute the majority of cells present: with much greater abundance and substantially better inter-cell communication capability. Sub-population analysis for this set of myeloid cells revealed that one class was the macrophage, which is a differentially-enriched cell type. In patients with recurrent erosive OLP, the TREM-1-high macrophage subset was highly enriched and showed a typical M1 polarization profile, with the M1 markers, which accounted for a high percentage (82.1%) . In addition, these cells had a high level of expression of IL-1 β . This result, obtained at the single-cell level, illustrates that TREM-1 similarly promotes myeloid cells to adopt a pro-inflammatory phenotype in non-infectious oral inflammatory environments. Follow-up studies found that TREM-1⁺ macrophages regulate the differentiation of downstream pathogenic Th17 cells by secreting IL-1 β , and this effect was fully inhibited when an IL-1 β neutralizing antibody was added.

Additionally, in the lesional tissue of oral lichen planus, pyroptotic epithelial cells, TREM-1⁺ macrophages, and Th17 cells were spatially colocalized. Enhanced interaction among these three kinds of cells constructed a self-sustaining pathological cycle, which finally led to epithelium destruction. TREM-1 acts as a shared central node that converts initial stimuli into "destructive inflammation" across periodontitis, peri-implantitis, and oral lichen planus. No matter whether the upstream driving factors come from microbe-associated PAMPs or endogenous DAMPs, the TREM-1 axis helps promote the pro-inflammatory polarization of myeloid cells, boosts systemic and local cytokine networks, and turns on pathways related to matrix degradation and bone resorption^[43].

This process eventually leads to the disruption of local oral immune homeostasis and the damage of oral tissues. This common cross-disease mechanism provides a solid theoretical basis for TREM-1 to serve as a therapeutic target for oral inflammation and as a bridge molecule connecting oral and systemic diseases.

4 TREM-1 in systemic diseases

TREM-1 acts as a typical inflammatory amplification receptor; by regulating the inflammatory cascades mediated by myeloid cells, it affects the occurrence and development of acute infectious diseases, metabolic disorders, cardiovascular diseases, autoimmune diseases, and neurodegenerative diseases.

As such, it is recognized as a key signaling node that connects local inflammation to systemic pathological damage^[44,45].

4.1 TREM-1 aggravates the inflammatory response in sepsis

Sepsis is the dysregulated response of the host to an infection resulting in life-threatening organ dysfunction. Central to this disease is an unchecked inflammatory response resulting from the

systemic spread of a localized infection^[46]. In cases where sepsis is present, TREM-1 expression at the cell surface in myeloid cells (including neutrophils and monocytes/macrophages) is significantly elevated^[3]. Sepsis provides an excellent example of the fundamental pathophysiological mechanism by which TREM-1 facilitates the transition from local infection to a widespread dissemination of inflammation. In septic conditions, the expression of TREM-1 on the surface of myeloid cells like neutrophils and monocytes/macrophages is significantly elevated^[47]. Mult-microbial infection induced by cecal ligation and perforation leads to a 3 to 5-fold increase in TREM-1 expression levels in peripheral blood and peritoneal macrophages^[48].

During the progression of sepsis, the TREM-1-mediated "phenotypic reprogramming" of myeloid cells mainly takes the form of promoting macrophages to shift toward the M1 pro-inflammatory phenotype. In a sepsis-related acute lung injury model induced by LPS stimulation, LPS triggers M1 polarization of alveolar macrophages. Nevertheless, knockdown of TREM-1 dramatically attenuates that polarization and hence ameliorates lung tissue injury. TREM-1 also blocks the polarization of macrophages toward the M2 anti-inflammatory phenotype. In a model of sepsis-associated acute renal failure, TREM-1 deficiency also activates the PI3K/AKT pathway and the STAT6 pathway, which results in the activation of IRF4. This activation subsequently promotes M2 anti-inflammatory polarization of macrophages, along with increased expression of the anti-inflammatory factors interleukin-10 (IL-10) and cluster of differentiation 206 (CD206)^[48,49].

When TREM-1 interacts with PAMPs/DAMPs, it switches on Syk kinase and downstream signaling cascades through its adaptor protein DAP12. This process strongly stimulates the quick secretion of proinflammatory factors, including IL-1 β , TNF- α , and IL-6. Clinical investigations demonstrate a strong positive correlation between serum sTREM-1 concentrations and IL-6/IL-10 expression in patients diagnosed with sepsis^[50]. What's more, the TREM-1 and TLR signaling pathways work together to produce obvious synergistic amplification effects^[51], quickly turning localized defense responses into systemic inflammatory storms.

The "distant seeding effect" of TREM-1 is revealed by the elevation in systemic levels of inflammatory mediators as well as by damage of distant parenchymatous organs directly. During sepsis, TREM-1 activates the NLR family pyrin domain containing 3 (NLRP3) inflammasomes through the Structural maintenance of chromosomes 4 (SMC4)/NF- κ B essential modulator (NEMO) pathway, which in turn induces pyroptosis of cardiomyocytes. Stimulation with LPS notably increases TREM-1 expression in HL-1 cardiomyocytes, while at the same time activating the activity of NLRP3, Gasdermin D, caspase-1, and IL-1 β . The TREM-1 inhibitor LR12 effectively reduces cardiomyocyte pyroptosis, enhances cardiac function, and extends the survival time of animals.

These results illustrate that TREM-1 is not only a key inflammatory receptor on the surface of myeloid cells but also directly impairs non-immune cells such as cardiomyocytes. As such, it acts as a critical molecular link connecting systemic inflammatory responses to specific organ dysfunction^[52]. TREM-1 is capable of reshaping the phenotype of myeloid cells, triggering a cytokine storm, and ultimately causing damage to distant organs^[8]. This pathological process shows clear similarities to the mechanism in oral inflammation, where local inflammatory activation leads to

effects in distant parts of the body.

4.2 TREM-1 in the pro-inflammatory paradigm of chronic inflammatory diseases

4.2.1 Atherosclerotic cardiovascular disease

Atherosclerosis is defined as a chronic vascular inflammatory condition driven by lipid deposition and immune responses^[53]. TREM-1 is present in endothelial cells, monocytes/macrophages, smooth muscle cells, and platelets, with its expression significantly increased in atherosclerotic plaques—especially in lipid-rich vulnerable plaque areas. When TREM-1 is activated, it aggravates subendothelial lipid accumulation and triggers the secretion of proinflammatory factors such as IL-1 β and TNF- α . These proinflammatory factors further promote the upregulation of TREM-1, forming a positive feedback amplification loop^[54]. TREM-1 up-regulates the production of MMP-1 and MMP-9, which promote collagenolytic activity and fibrous cap thinning, leading to plaque instability and rupture. Interventional studies provide reverse validation: knockout of the TREM-1 gene or pharmacologic blocking, e.g., with the LR12 peptide, significantly reduces atheromatous plaque area, and reduces intraplaque inflammation. TREM-1 inhibitors may stabilise vulnerable plaques, which points to them being promising therapeutic targets^[55]. This pathway, which starts with the activation of myeloid cells and the subsequent release of inflammatory cytokines and ends with plaque destabilization caused by matrix degradation, bears striking similarities to the pathogenic mechanisms underlying oral inflammation.

4.2.2 Diabetic Nephropathy

Several comprehensive review papers have demonstrated that both inflammation and fibrosis are fundamental processes driving Diabetic Nephropathy (DN) development^[56], with mutual interactions between immune-inflammatory reactions and metabolic diseases existing throughout the whole period of the illness^[57]. The diabetic nephropathy is a good example of kidney damage mediated by the TREM-1-induced macrophage phenotype change^[9]. High glucose significantly enhances TREM-1 expression in kidney resident macrophages, and TREM-1 level positively correlates with inducible nitric oxide synthase (iNOS), specific for M1 macrophages. High glucose induces TREM-1 transcription through phosphorylation of STAT-1, which in turn promotes polarization of macrophages toward pro-inflammatory phenotypes and prevents the development of anti-inflammatory M2 phenotypes.

In functional experiment studies, they found that treatment with TREM-1 siRNA could totally reverse the M1 polarization caused by high glucose, which was accompanied by decreased iNOS expression and recovered MR expression, which validates that TREM-1 plays a key role in driving this switch in phenotype. Activated TREM-1 signaling further promotes the secretion of proinflammatory factors such as TNF- α and IL-1 β , initiating a vicious cycle of "hyperglycemia-inflammation-tissue damage." Analysis of clinical samples revealed a positive correlation between the number of infiltrating M1 macrophages in renal tissue and the severity of glomerulosclerosis and interstitial fibrosis.

At the same time, TREM-1 expression levels were directly related to the rate of renal function decline^[58,59]. TREM-1 activation encourages the synthesis and secretion of classic proinflammatory

mediators like IL-1 β and TNF- α ^[33]. As a key downstream effector molecule in the TREM-1 signaling pathway, TNF- α has been shown to induce serine phosphorylation of insulin receptor substrate (IRS), directly disrupting insulin signaling pathways.

It acts as a core mediator connecting obesity-related inflammation to insulin resistance in type 2 diabetes. In this context, the sustained activation of the TREM-1 pathway promotes the release of proinflammatory factors such as TNF- α through cascade amplification. It also forms a positive feedback loop with high-glucose environments, thus becoming a key driver of the vicious cycle of "hyperglycemia-inflammation-insulin resistance"^[60].

4.2.3 Inflammatory bowel disease

Studies related to inflammatory bowel disease (IBD) have also added to the list of how TREM-1 can promote tissue injury. Increased TREM-1 expression in intestinal macrophages isolated from IBD patients during an acute episode of the disease. Additionally, the degree of TREM-1 expression correlated with disease activity as well as an adverse response to infliximab treatment.

Overexpression of TREM-1 first reshapes the functional phenotype of macrophages, weakening the ability of TREM-1-high monocytes to differentiate into M2-type regulatory macrophages. At the same time, it activates the E3 ubiquitin ligase Itchy E3 ubiquitin protein ligase (ITCH) via the DAP12/SYK pathway, which in turn causes Transforming growth factor- β -activated kinase 1 (TAK1) ubiquitination and degradation, triggering caspase-8-dependent pyroptosis in macrophages. Macrophages undergoing pyroptosis release large quantities of proinflammatory factors, which not only worsen intestinal inflammation and tissue damage but also reduce the therapeutic effectiveness of anti-TNF- α monoclonal antibodies. Functional experimental studies show that colitis mice with TREM-1 overexpression displayed resistance to infliximab treatment. On the other hand, inhibition of pSYK or knockdown of ITCH recovered TAK1 levels, decreased macrophage pyroptosis, and ameliorated therapeutic effects. Clinical sample analysis showed that TREM-1 expression was dramatically increased in intestinal macrophages from Crohn's disease and ulcerative colitis patients, promoting an increased inflammatory response through the secretion of TNF- α and IL-6. Blocking TREM-1 notably reduced the severity of experimental colitis^[61].

Based on these findings, TREM-1 plays a central role in intestinal tissue destruction and treatment resistance by regulating macrophage phenotype remodeling and pyroptosis-mediated release of proinflammatory factors. This pathological process is consistent in nature with the role of TREM-1 during oral inflammation, and it can be assumed therefore that TREM-1 could play an integrative role between local oral inflammation and systemic inflammatory disease.

4.2.4 Alzheimer's disease

The pathophysiological role of TREM-1 in AD is no longer limited to merely exacerbating inflammation but has been shown to be part of an intricate web involving derangement of the metabolism-immunology axis, peripheral-central communications, and intercellular conversations; TREM-1 induces metabolic reprogramming of myeloid cells, which inhibits the Pentose Phosphate Pathway (PPP) and therefore reduces the supply of Ribose-5-phosphate (R5P)^[62]. This disruption impairs nucleotide

synthesis and mitochondrial respiration, putting myeloid cells in an energy crisis and making them lose their normal functional phenotype—including reduced ability to phagocytose A β . On this basis, TREM-1 not only boosts neuroinflammation through classic downstream pathways but also serves as a key node in the eCIRP-TREM-1 axis^[63]. This axis regulates the transformation of astrocytes into the neurotoxic A1 type that promotes the release of toxic factors (e.g. complement C3) thereby aggravating neuronal damage and synapse loss, promotes cell senescence. Peripheral macrophages express high levels of TREM-1, and TREM-1 deficiency rescues the senescent phenotype in these macrophages^[63].

In the central nervous system (CNS), TREM-1 and Iba1+ myeloid cells co-localize around amyloid plaques, and their protein levels are positively correlated to Braak staging and neurofibrillary tangles density; clinical data also support this mechanism: CSF sTREM-1 level was significantly higher in people with cognitive impairment, and baseline correlates with positive correlation of hippocampal atrophy rate^[62].

Mendelian randomization analysis also points to a positive causal relationship between plasma sTREM-1 and AD risk^[64]. TREM-1 drives myeloid cell dysfunction through metabolic reprogramming, promotes the transition of glial cells to a toxic state, and accelerates neuroinflammation and synaptic damage via peripheral-central synergistic mechanisms.

In summary, TREM-1 causes myeloid cell dysfunction through metabolic reprogramming. It promotes toxic changes in glial cells. It accelerates neuroinflammation and synaptic injury by coordinating peripheral and central signals. These effects finally lead to hippocampal atrophy and cognitive decline. TREM-1 is a key

molecular hub linking energy metabolism, neuroimmunity, and neurodegeneration.

4.2.5 Rheumatoid arthritis

The role of TREM-1 in rheumatic immune diseases appears to be quite complicated: Activated TREM-1 in RA promotes the expression of the transcription factor E2F transcription factor 1 (E2F1), which then modulates the expression level of TOMM40, a transporter that resides at the outer mitochondrial membrane. This adjustment results in impaired mitophagy in macrophages and an excessive buildup of reactive oxygen species (ROS), which speeds up synovial inflammation and joint bone destruction. Blocking TREM-1 signaling to some extent restores mitophagy function and reduces local inflammatory responses^[65].

TREM-1 cooperates with the toll-like receptors pathway to promote the production of inflammatory mediators. TREM-1 promotes the release of many proinflammatory cytokines, including tumor necrosis factor-alpha (TNF- α) and interleukin-1 beta (IL-1 β), while simultaneously inhibiting the synthesis of the anti-inflammatory cytokine, IL-10. This creates a positive feedforward loop to amplify synovial inflammation within RA^[63].

5 TREM1-mediated oral-systemic inflammation dissemination

As summarized in Table 1, TREM-1 exhibits strikingly similar pathogenic roles across oral and systemic inflammatory diseases, acting as a common amplifier of inflammation. This shared mechanism provides the molecular basis for TREM-1 to function as

Table 1 TREM-1 as a common inflammatory amplifier in oral and systemic diseases.

Field	Disease	Function	Evidence/Key Findings	References
Oral Inflammation	Periodontitis	- Promotes M1 macrophage polarization - Enhances pro-inflammatory cytokine release - Drives alveolar bone resorption	- TREM-1 upregulated in gingival tissues; correlates with clinical severity - Trem1^{-/-} mice exhibit reduced bone loss	[23,24,33,36]
	Peri-implantitis	- Activates TREM-1/PGLYRP1/MMP-8 axis - Links microbial burden to extracellular matrix degradation	Salivary sTREM-1, PGLYRP1, MMP-8 levels are comparable to periodontitis	[40]
	Oral Lichen Planus	- TREM-1⁺ macrophages drive Th17 differentiation via IL-1β - Forms self-sustaining inflammatory cycle with pyroptotic epithelial cells	- TREM-1⁺ M1 macrophage enrichment (82.1%) - IL-1β neutralization completely blocks Th17 activation	[43]
Systemic Diseases	Sepsis	- Amplifies inflammation via M1 polarization - Triggers cytokine storm - Induces distant organ damage (heart, lung, kidney)	- TREM-1 expression is increased by 3- to 5-fold in sepsis - TREM-1 knockdown attenuates lung injury - LR12 inhibits cardiomyocyte pyroptosis and prolongs survival	[47,48,79]
	Atherosclerosis	- Activates macrophages - Increases MMP-1/9 expression - Promotes plaque instability	- TREM-1 is upregulated in vulnerable plaque regions - TREM-1 knockout or LR12 treatment reduces plaque area and intraplaque inflammation	[54,55]
	Diabetic Nephropathy	- Promotes M1 macrophage polarization via STAT1 - Initiates the hyperglycemia-inflammation-tissue damage cycle	- High glucose induces TREM-1 expression - TREM-1 siRNA reverses M1 polarization	[58,59]
	Inflammatory Bowel Disease	- Induces macrophage pyroptosis via DAPI2/SYK/ITCH pathway - Causes tissue damage and anti-TNF resistance	- TREM-1 is overexpressed in intestinal macrophages - ITCH knockdown restores TAK1 levels and improves therapy response	[61]
	Alzheimer's Disease	- Disrupts myeloid cell metabolism (inhibits PPP) - Impairs Aβ phagocytosis - Promotes neurotoxic A1 astrocytes	- CSF sTREM-1 elevated - Correlates with hippocampal atrophy rate - Mendelian randomization supports a causal relationship with AD risk	[62,64]
	Rheumatoid Arthritis	- Impairs mitophagy via the E2F1/TOMM40 axis - Leads to ROS accumulation and joint destruction	- TREM-1 activates E2F1 - TREM-1 blockade restores mitophagy and reduces synovial inflammation	[65]

a bridge linking local oral inflammation to systemic pathological conditions. The epidemiological connections between oral inflammatory conditions and various chronic systemic inflammatory diseases have been verified time and again, but the underlying molecular and cellular mechanisms have not yet been fully elucidated. This chapter establishes a TREM-1-mediated "oral-systemic" inflammatory connection network.

As an upstream driver of inflammatory amplification and barrier disruption, TREM-1 is capable of promoting systemic low-grade inflammation and organ impairment through three distinct pathways: "leakage of inflammatory mediators," "migration of TREM-1⁺ immune cells," and "synergistic interaction with systemic metabolic risk factors." In this network, sTREM-1 is an indicator that can be measured in whole-body disease load, which has possible diagnostic and prognostic value; it also shows that TREM-1 plays a central role in regulating multiple organs: linking regional oral inflammation to systemic pathophysiological injury described above.

5.1 Inflammatory mediator leakage

Once the epithelial barrier is disrupted, viable bacteria and their metabolic products, such as LPS together with local inflammatory mediators, can pass through the ulcerated epithelial tissue and enter the subgingival vascular network^[66-68]. This leads to either transient or persistent bacteremia or endotoxemia. The PAMPs, as well as the inflammatory mediators, which enter the systemic circulation, pass from the blood stream to the liver, where they drive production of acute-phase proteins^[69], induce expansion and secretion by myeloid progenitor cells, and exert effects upon vascular endothelial cells, increasing the expression of adhesion molecules, thus promoting the acceleration of leukocyte adhesion and migration^[70]. This cascade of events represents the biological basis for the development of systemic low-grade inflammation, which produces an inflammatory milieu that promotes the onset of pathologic conditions such as atherosclerosis or insulin resistance^[71].

signals to all parts of the body. As an important non-canonical inflammatory mediator, neutrophil extracellular traps (NETs) directly participate in and aggravate inflammatory damage of local tissues via physical and chemical mechanisms. Under the action of mature bacterial biofilms, NETs undergo a conformational transition from DNase I-sensitive B-DNA to degradation-resistant Z-DNA. They thereby act as a persistent nucleation scaffold to facilitate apatite deposition and drive dental calculus formation. NETs provide a nucleation scaffold for apatite deposition, whereas an adequate phosphate substrate is another prerequisite for mineralization^[72]. By promoting NET release, TREM-1 may indirectly provide more nucleation sites for this phosphate-dependent pathological mineralization. Therefore, NETs are not only products of host immune defense, but also directly mediate pathological mineralization and structural destruction of local tissues^[73]. Activation of TREM-1 can significantly boost the release of NETs and serve as one of their structural components. Pharmacological inhibition or genetic knockout of TREM-1 can effectively reduce NETs formation. In systemic diseases such as sepsis, NETs induce endothelial cell activation and impair vascular function. Inhibition of TREM-1 alleviates these adverse effects and thus exerts protective effects^[74]. TREM-1 potentiates the release of inflammatory mediators, directly mediating local tissue damage and inhibiting TREM-1 alleviates the resulting vascular dysfunction and confers protection.

In addition, it is interesting that in studies on periodontitis, there was also a correlation with higher levels of serum TREM-1 and modified levels of PGLYRP1^[75], which can serve as clinical evidence supporting this molecular mediation process. A local oral stimulus leads to an increase in TREM-1 ligand levels, which activates the TREM-1 signaling axis.

5.2 Long-range effects of TREM-1⁺ immune cells

Chronic oral inflammatory foci act not only as sources of bacteria and inflammatory mediators but also as "training grounds" for immune reprogramming that are abundant in PAMPs and DAMPs. Infiltrating myeloid cells undergo epigenetic remodeling under TREM-1 activation and other inflammatory signals, gaining a stable pro-inflammatory response tendency^[76]. Certain "preactivated" myeloid cells can break away from oral lesions through lymphatic or blood circulation, entering the peripheral circulatory system^[76]. These cells show reduced response thresholds and enhanced reactivity to secondary stimuli, secreting large quantities of inflammatory mediators while attracting other immune cells. This process expands existing lesions or induces the formation of new lesions in distant organs^[77].

In the lesion sites of various systemic inflammatory diseases, infiltration of myeloid cells with high TREM-1 expression can be observed. Intestinal-derived TREM-1-positive macrophages are activated after cardiac arrest and cardiopulmonary resuscitation, and migrate to the brain via blood circulation, acting as crucial signal carriers linking intestinal injury to secondary brain damage. These TREM-1-signaling cells exacerbate neuroinflammation in the brain, facilitate neuronal injury and glial cell activation, and consequently lead to functional and structural damage to the distant organ, namely the brain^[78]. Peripheral TREM-1-positive myeloid cells act as cellular signal carriers to indirectly affect the central nervous system through systemic inflammatory responses, resulting in functional damage to distant brain regions. In aging and Alzheimer's disease models, TREM-1-mediated peripheral immune-metabolic disorders and inflammatory factor release are sufficient to induce hippocampus-dependent cognitive impairment. Conversely, TREM-1 depletion restores systemic immune homeostasis and exerts protective effects on brain function.^[62]

These findings indicate that, in addition to bacterial products and inflammatory mediators, TREM-1⁺ immune cells themselves may act as "cellular carriers." They remotely deliver signals related to inflammation and aging along the oral-peripheral-target organ axis, further enriching the TREM-1-mediated "oral-systemic" inflammatory linkage network proposed in this chapter.

5.3 Synergistic amplification of TREM-1 and systemic risk factors

TREM-1 signals from the mouth frequently coexist with systemic metabolic risk factors such as hyperglycemia, dyslipidemia, and obesity, creating a positive feedback loop that gradually exacerbates the inflammatory response. Hyperglycemia and lipid metabolism disorders may directly aggravate inflammation by inducing oxidative stress and activating NF- κ B.

In atherosclerosis models, a high-fat diet in combination with hypoxia leads to an increase in TREM-1 levels, accelerating plaque development and increasing the likelihood of plaque rupture^[51]. Here, the chronic low-level inflammasome burden induced by periodontal disease coupled with peripheral endocrinopathy

promotes propagation of the inflammasome into vessels, kidney, and nervous system^[73].

This synergy of amplification by oral TREM-1 signal with the systemic metabolic risk factor reinforces the TREM-1-mediated "oral-systemic" link of inflammation, which is considered the third. The major route by which oral inflammation extends to other distant organs, and may provide an explanation for the clinical association of oral diseases with systemic metabolic disorders.

Systemic metabolic abnormalities can also adjust TREM-1 downstream signaling thresholds via pathways such as phosphatase activity regulation and microRNA networks, boosting the "inflammatory output gain" effect when TREM-1 is activated^[80]. In this way, the TREM-1 axis not only acts as a link connecting oral-local inflammation to systemic diseases but also serves as a critical connector between metabolic risk states and the inflammatory network. Targeting the TREM-1 pathway may thus represent a promising strategy to break the vicious cycle linking metabolic disorders and chronic inflammation. Modulating this axis could offer novel therapeutic potential for both oral inflammatory lesions and related systemic complications. In conjunction with systemic metabolic risk factors, it is the central driver module for propagating oral inflammation to systemic sites (Fig. 2). As a quantitative marker, sTREM-1 represents the activity state of this driver module systemically, which is a biomarker to measure the disease burden and response to therapy.

6 Intervention strategies targeting TREM-1

Existing basic and preclinical research findings demonstrate that the TREM-1 axis exerts a common "inflammation amplification" function across diverse local and systemic inflammatory contexts. This provides solid theoretical support for its role as a promising therapeutic target. In summary, we propose that incorporating oral inflammation control in the treatment strategy of chronic diseases by tackling the basal inflammatory burden associated with the

TREM-1 axis has huge potential for breaking the vicious coupling between oral inflammation and metabolic risk factors. This approach offers integrated molecular signals to decipher the common pathophysiological basis of several chronic inflammatory co-morbidities, and the identification of possible targets for interventions to prevent multisystem disease among those at risk.

Supporting evidence mainly comes from two aspects: first, pharmacological methods using receptor antagonist peptides and small-molecule pathway modulators; second, comprehensive intervention measures based on oral local treatment combined with TREM-1 axis downregulation.

6.1 Pharmacological blockade: receptor antagonism and signaling pathway regulation

TREM-1 receptor activity is inhibited directly by the use of peptide receptors as antagonists for inhibiting inflammation cascade reactions. Animal studies in periodontitis, local application of the TREM-1 antagonist peptide LP17 significantly decreased alveolar bone resorption and downregulated the levels of IL-1 β , IL-17A, and the RANKL/OPG ratio of lesion tissue^[48]. Inspired by these findings, recent studies have demonstrated the potential of nanomaterials such as RNA-amorphous calcium phosphate in promoting periodontal bone repair^[81]. In vitro research also confirmed that *Porphyromonas gingivalis* lipopolysaccharide enhances TREM-1 expression in human monocytes, thereby inducing the secretion of IL-1 β , TNF- α , and IL-8. The TREM-1 inhibitory peptide Nangibotide (LR12) partially reversed these proinflammatory effects^[50].

In terms of systemic diseases, LR12 reduced the levels of proinflammatory factors and alleviated tissue damage in animal models of sepsis. However, it failed to fully achieve the prespecified endpoints in Phase II clinical trials^[51]. This suggests that in complex systemic inflammatory environments, the therapeutic benefits of single-pathway blockade may be affected by disease stage,

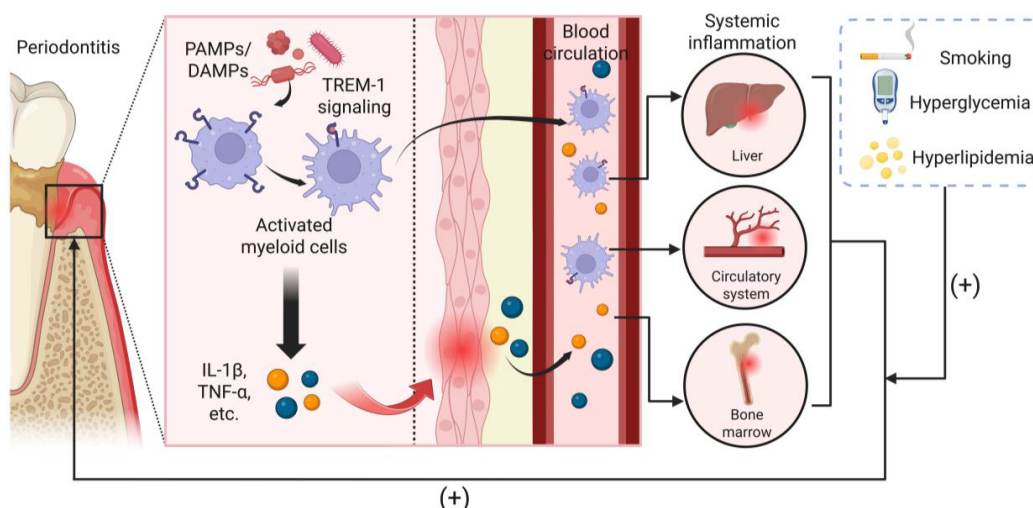


Figure 2 TREM-1 mediates the bidirectional pathological crosstalk between periodontitis and systemic inflammation. TREM-1 plays a pivotal role in mediating the transition of oral inflammation to systemic diseases. Locally in the oral cavity, periodontitis prompts myeloid cells to recognize PAMPs/DAMPs, which activates TREM-1 signaling. This pathway drives M1 macrophage polarization and the excessive release of proinflammatory cytokines (e.g., IL-1 β , TNF- α), amplifying the local inflammatory response, causing tissue destruction, and impairing the periodontal barrier. Consequently, bacterial products, inflammatory mediators, and TREM-1⁺ myeloid cells enter the systemic circulation. These cells migrate to distal organs (e.g., liver, blood vessels, bones), remodeling the local immune microenvironment and inducing systemic low-grade inflammation. Furthermore, these TREM-1-dependent effects synergize with metabolic risk factors. These factors exacerbate systemic inflammation, which in turn amplifies periodontal inflammation, forming a pathological positive feedback loop.

etiological factors, and comorbid risk factors. At present, clinical studies that systematically evaluate the efficacy of TREM-1 inhibitors in populations with "oral inflammation combined with systemic chronic diseases" are still lacking, leaving an important gap for future translational research.

Besides direct receptor antagonism, there are also some small molecule drugs that could exert anti-inflammatory effects through regulation of the TREM-1-related signaling pathway. In a rat ligature-induced periodontitis model, the sEH inhibitor TPPU significantly ameliorated alveolar bone loss, which was associated with downregulation of TREM-1 mRNA, IL-1 β , and TNF- α in the periodontal tissue, together with less infiltration of inflammatory cells^[79]. Sub-antimicrobial-dose doxycycline has been shown to inhibit the upregulation of TREM-1 induced by *Porphyromonas gingivalis*^[82]. This finding suggests that the anti-inflammatory effects of certain traditional drugs may be mediated through the TREM-1 axis. Such "indirect regulation" strategies are mostly limited to animal and in vitro research, and their specificity, safety, and long-term application value still need further verification in clinical settings. In other systemic inflammation disorders, therapies aimed at targeting TREM-1 move away from a non-specific anti-inflammatory approach to more specific modulatory therapy. In addition to LR12, new inhibitors like GF9—which was developed with the SCHOOL model—can block TREM-1-DAP12 binding independent of ligand presence (Fig. 3).

In contrast to pan-TREM-1 blockade, restricted inhibition targeting only one or a subset of TREM-1-expressing cell type(s) such as macrophages is quite different in efficacy between these disease models^[83], which indicates an urgent need for better defined "cell-specific + time-specific" interventions to be developed in future translational studies to enhance treatment efficacy and minimize undesired side effects.

6.2 Oral local intervention and TREM-1 axis regulation

In the field of oral medicine, so far, most studies about TREM-1 are limited to diagnosis, but local targeted treatment remains at an initial stage. Many reports showed that sTREM-1 content in saliva and gingival crevicular fluids from chronic periodontitis patients was significantly elevated compared with those from gingivitis patients and normal periodontium subjects. This finding demonstrates promising diagnostic performance in distinguishing different degrees of periodontal inflammatory lesions. After patients receive subgingival scaling and root planing (SRP), sTREM-1 levels in gingival crevicular fluid drop sharply. This reduction is positively correlated with the decrease in specific periodontal pathogens (such as *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*)^[25], indicating a direct association between bacterial load and the activation status of local TREM-1. Sub-antimicrobial doses of doxycycline can inhibit the upregulation of TREM-1, and local injection of LP17 achieves a reduction in alveolar bone resorption. These results provide experimental evidence for the combined intervention strategy of standard mechanical treatment + TREM-1 targeted intervention.

Using an in vitro model established with a bone-vascular interface microfluidic chip, intervention on TREM-1 in endothelial cells partially improves vascular barrier dysfunction induced by LPS/TNF- α . This suggests that there may be an actionable intervention window along the "oral-vascular endothelium-systemic inflammation" axis^[84].

Based on existing research evidence, local oral treatments (such as SRP) serve as a fundamental approach to reduce the activation of the TREM-1 axis. Reasonably incorporating TREM-1-targeted drugs at this stage may help reduce the systemic inflammatory burden while controlling local oral diseases. However, optimal

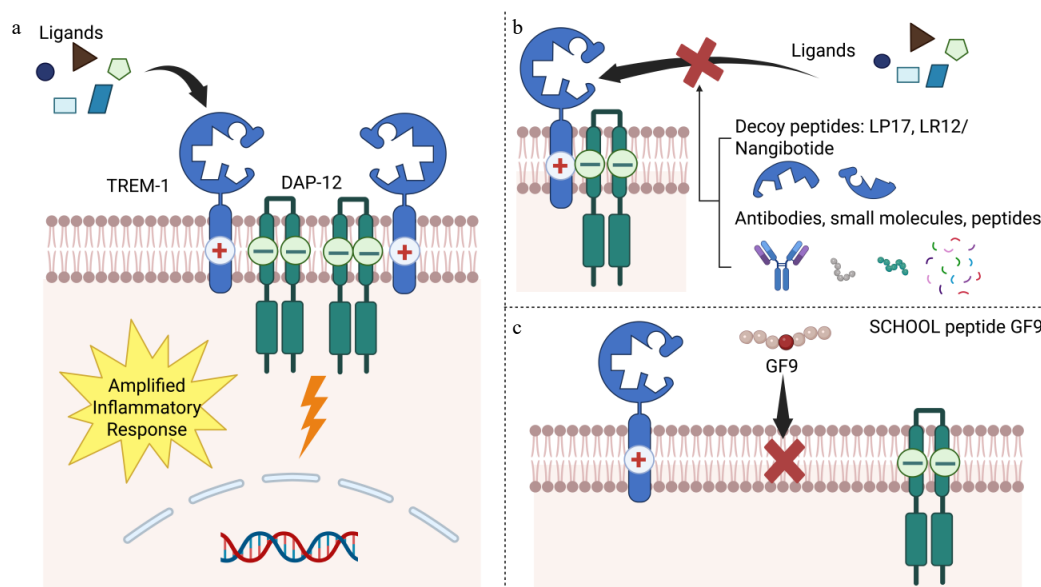


Figure 3 TREM-1: receptor assembly, signaling and mechanisms of ligand-dependent and ligand-independent inhibition. (a) TREM-1/DAP-12 receptor complex assembly and signaling are depicted. TREM-1 and DAP-12 are bound together by electrostatic interactions between their basic and acidic amino acids in the cell membrane. Binding to the known and unknown natural human ligands of TREM-1 results in dimerization/multimerization of the TREM-1/DAP-12 complex followed by homooligomerization of cytoplasmic DAP-12 domains that triggers the receptor. (b) LP17, LR12, and other antagonist peptides, along with small-molecule drugs, target TREM-1 either by preventing ligand engagement or by modulating downstream signaling, leading to reduced proinflammatory cytokine production. (c) Ligand-independent peptide inhibitor GF9 (SCHOOL mechanism-based peptide) disrupts the interactions between TREM-1 and DAP-12 in the cell membrane that upon binding to the ligands, results in dimerization/multimerization of only TREM-1 but not DAP-12, completely blocking the transmembrane signaling. GF9 can reach its site of action in the cell membrane from.

intervention methods (including administration routes, dosages, and frequencies), suitable beneficiary populations, and long-term safety still need to be systematically evaluated through prospective clinical trials, laying a solid foundation for the translational application of TREM-1-targeted local interventions in oral clinical practice.

7 Challenges and outlook

Although investigations over time have delineated TREM-1 as an essential actor in the oral-systemic-inflammatory web, moving from a "potential treatment option" to a "clinically viable approach" is still full of obstacles ranging from mechanistic studies, clinical translation, therapeutic application, or translational medicine, all of which need further investigation to translate TREM-1-related studies into the clinic.

7.1 Mechanistic level: the causal chain remains incomplete

Existing evidence mainly illustrates the "parallel pathogenic patterns" of TREM-1 across different organs and disease types^[4]. Yet, direct proof confirming the causal relationship that "oral TREM-1 activation drives pathological changes in distant organs" is still insufficient. Future research should integrate conditional Trem1 knockout models with oral-circulatory-target organ animal models, combined with single-cell and spatial transcriptomics technologies^[85].

These approaches will enable in situ and dynamic tracing of the origin, migration pathways, and functional destinations of TREM-1⁺ cells, thereby clarifying the relative contributions of local oral TREM-1 signaling versus systemic TREM-1 signaling in the development of systemic diseases. This will help fill the gap in the causal chain between oral inflammation and systemic pathological damage mediated by TREM-1.

7.2 Marker application: sTREM-1 alone exhibits limited specificity

sTREM-1 is highly sensitive for alterations in the inflammatory condition; however, it may increase not only during infection but also under specific non-infectious inflammatory conditions as well, which diminishes its potential to identify the source of inflammation and organ-specificity along the "oral-systemic comorbidity axis". Further research is needed to determine whether combining multiple markers into a model, such as sTREM-1+PGLYRP1+IL-1 β +MMP-8, adds further information for risk prediction or outcome assessment in larger prospective studies."

Quantified periodontal status should be incorporated into the analytical framework, linking biomarker profiles to cardiovascular and renal clinical endpoints, to verify their practical clinical applicability. This will improve the accuracy of sTREM-1 in distinguishing oral-derived systemic inflammation from other systemic inflammatory responses.

7.3 Therapeutic translation: balancing anti-inflammation and host defense

TREM-1 is an important pro-inflammatory mediator, but it has also been shown to play a role during host defence responses. Thus, modulating TREM-1 activity without impairing normal physiological processes may be difficult and a critical target for

future therapies. However, so far, most studies have been performed in patients with short-term illnesses (e.g., sepsis), and lack systematic evidence on chronic inflammatory diseases and/or populations with systemic-oral related comorbidities^[86].

Further studies are needed, particularly designing randomized clinical trials to compare conventional treatment against periodontal treatments based on TREM-1 modulation; second, to assess the influence of improved oral management on sTREM-1 level and systemic clinical outcome among high-risk groups, such as those with cardiovascular disease, and diabetic nephropathy^[87].

Third, explore TREM-1 inhibition approaches with different intensities, delivery routes, and target cell specificities (for example, confined to the oral cavity or specific myeloid cell subsets) in small-scale populations. This will help define safety margins and identify optimal beneficiary groups, laying the groundwork for the clinical translation of TREM-1-targeted interventions in oral-systemic comorbidities^[25].

8 Summary

As a key immune regulatory receptor on the surface of myeloid cells, TREM-1 plays a central role as a "molecular amplifier" in the amplification of inflammatory cascades through its synergistic interaction with signaling pathways such as TLR. This paper systematically clarifies the pathogenic mechanisms of TREM-1 in local oral inflammation: it promotes tissue destruction and bone resorption by inducing M1 macrophage polarization, the release of pro-inflammatory factors, and matrix degradation.

What matters more here, however, is its high reproducibility among different systemic inflammatory diseases, implying TREM-1 might serve as a general molecular node linking local oral immune dysregulation with systemic pathological change. The same pathogenic pattern in turn verifies the cross-organ regulatory role of TREM-1, which fits well with the role it has already been described to have in both oral and systemic inflammation.

TREM-1 promotes the spread of inflammation in three ways. Firstly, local mediators of inflammation and bacterial antigens are released into the bloodstream, inducing systemic low-grade inflammation. Secondly, remote migration of TREM-1⁺ myeloid cells reshapes the immune microenvironment of distal organs; thirdly, cooperation with metabolic risk factors enhances inflammation production. Its soluble form, sTREM-1, is an indicator which may reflect local or systemic inflammatory burden stably and could be used to evaluate both oral and systemic disease by diagnosis/prognosis prospectively, consistent with previous observations on its clinical usefulness in evaluating inflammation status and response to therapy indicated by sTREM-1 levels.

On an interventional basis, TREM-1-targeted antagonist peptides and signal transduction modulators have shown promise in experimental studies as a way to reduce inflammation and subsequent organ injury. Concomitant use of TREM-1-targeted therapies to standard treatment in the mouth, such as subgingival scaling, may be very useful because it might treat both the lesion locally within the mouth and reduce inflammation systemically: offering new prevention and treatment approaches to "oral-systemic comorbidities."

However, there are still some issues in existing works, such as a lack of an explanation about how it works, limited specificity of sTREM-1 alone as a marker, and undefined therapeutic time windows of TREM-1-targeting strategies. Further studies must be

conducted using single-cell omics, spatial transcriptomics, and conditional knockout models in order to further decode the dynamic role of TREM-1 in the oral-local-systemic axis.

In conclusion, the TREM-1 may represent an ideal gateway to link oral medicine and systems disease research, providing a platform to advance the theory and practice of early detection, risk profiling, and targeted treatment of co-morbid chronic inflammation.

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Data available statement

Data will be made available on request.

Author contribution

M.Lu. guided and revised the manuscript. M.L. wrote the manuscript; M.T. and Y.H. contributed to making figures; M.L. searched for articles; M.Lu. revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent

N/A

Consent for publication

All authors have reviewed and approved the manuscript for publication.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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