Review Article

Regulatory T cells – The key immunoregulatory components in the pathophysiology of periodontal diseases: A review

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Abstract

Background: Periodontitis is a chronic immuno-inflammatory disease that alters the microbial-host interactions. The extent of periodontal damage is influenced by specific types of CD4+ T cells, including Th17 cells and Tregs, which respectively promote or inhibit the immune response. **Aim and objectives:** This study aims to explore the connection between Tregs and their immune-regulating factors in the development of periodontal diseases. The precise role of Tregs in periodontal disease remains a topic of debate, and this research seeks to contribute to a clearer understanding of their involvement. **Materials and Methods:** To pertain the relationship between the Tregs and immunoregulatory elements in the pathogenesis of periodontal diseases, a literature search was performed in PubMed/MEDLINE, Scopus, Google Scholar, and Web of Science. Data from case-control, cohort studies, literature, randomized controlled trials, and systematic reviews were included. **Review Results:** The study included 45 articles. Evidence regarding the exact role of Tregs in periodontal disease is still disputed. Tregs play a role in periodontal homeostasis and its upregulation shown to increase the anti-inflammatory cytokines. **Discussion:** Tregs exhibit distinct functional characteristics, such as balancing inflammation, performing antigen-specific functions, and regulating the activation and function of immune responses. They play a crucial role in defending against infections and controlling autoimmune diseases. Disruption in Treg cell regulation in periodontal disease may result in periodontal tissue destruction, and an imbalance between Th17 and Treg cells can contribute to the progression of periodontal disease. A limitation of this study is the lack of extensive human trials. **Conclusion:** Tregs play a role in periodontal homeostasis, and its upregulation has been shown to increase the anti-inflammatory cytokines. Thus, key elements such as Foxp3 (forkhead/winged-helix), a transcription factor, its suppressive function of Tregs mediated by TGF-β and interleukin -10 play a regulatory role in periodontal diseases. **Clinical significance**: Thus, key elements such as Foxp3, a transcription factor.

Keywords: periodontitis, regulatory T-lymphocytes, T helper 17 cells, transcription factors

Introduction

Periodontal disease is marked by inflammation caused by the interaction between the host and microbes, which can result in the destruction of tooth-supporting structures[(1)]. The rate of periodontal tissue breakdown is determined by the host immunoinflammatory responses, particularly the CD4+ T-cells mediated cellular responses[(2)]. When there is a disturbance in this immunoinflammatory homeostasis, evidence shows that there are distinct patterns of immune responses, including proinflammatory, Th1, and Th17 cytokines, which can amplify inflammation and mediate osteoclastogenesis in vivo, resulting in periodontal tissue destruction[(3,4)]. Different subsets of CD4+ T cells influence the host response during the progression of periodontitis by secreting cytokines that either promote or suppress this response[(5,6)]. The development of periodontitis is significantly influenced by two CD4+ cell subsets: Th17 (T helper 17) cells and Tregs (Regulatory T lymphocytes) are types of immune cells with different functions. Th17 cells produce IL-17, which is found in large amounts at inflammation sites. IL-17 not only triggers more inflammation but also increases bone loss by boosting Receptor Activator Nuclear Kappa Ligand (RANKL) on osteoblasts, highly expressed at inflammation sites, where it both induces proinflammatory cytokines and directly enhances osteoclastogenesis by upregulating factors that contribute to bone resorption in periodontitis[(7)]. In contrast, the T-cell subset, which has regulatory properties called Tregs, is involved in the suppression of inflammation or infection[(5)]. Tregs are considered key immunoregulatory elements due to the presence of a low abundance of leukocyte subsets that have a broad effect on the immune system[(8)]. Tregs are provided with unique functional properties such as balancing the inflammation and antigen-specific function, specifically regulating the activation, proliferation, and effector functions, thereby playing a role in regulating the immune responses with defense against infections and control of autoimmune diseases[(9,10)]. Among the CD4+ cell population, approximately 15% are thought to be Treg cells, which are vital for maintaining periodontal health. An abundance of Tregs is linked to the maintenance of bone health, even when there is local inflammation.[(11)] The transcription factor foxp3

(forkhead/winged-helix) has been identified as a specific marker for Treg cells, playing a regulatory role in periodontal diseases[12]. T-regulatory lymphocytes have been observed in periodontal lesions, with the presence of phenotypic markers such as IL-10, Foxp3, and TGF-β[13]. Thus, Tregs directs a new way to the therapeutic approaches that may potentially mitigate the immune-mediated inflammatory response and reestablish the periodontium equilibrium during periodontitis.periodontitis. The aim of this study was to explore the association between Tregs and key immunoregulatory factors in the development of periodontal diseases.

Materials And Methods

A comprehensive literature search was conducted in PubMed/MEDLINE, Web of Science, Scopus, Google Scholar, and Web of Science to explore the relationship between regulatory T cells (Tregs) and immunoregulatory elements in the pathogenesis of periodontal diseases. The search utilized the following terms: "Tregs" (Mesh) or "periodontitis" (Mesh) and "chronic periodontitis" (Mesh) and "immune-regulatory." There were no restrictions on the publication years, and only articles in English were included. The search included data from case-control studies, cohort studies, literature reviews, randomized controlled trials, and systematic reviews. Articles that did not discuss Tregs and their role in periodontal homeostasis were excluded. After the initial literature review, 108 articles related to periodontitis and host immune T cells were identified. Following the removal of duplicates, 67 articles underwent title and abstract screening. Subsequently, the search was refined using keywords specific to Tregs, resulting in 45 articles for full-text screening. The process of article selection is illustrated in Figure 1. Data extraction was conducted by the author (A), and all collected data were reviewed by a second reviewer (AS).

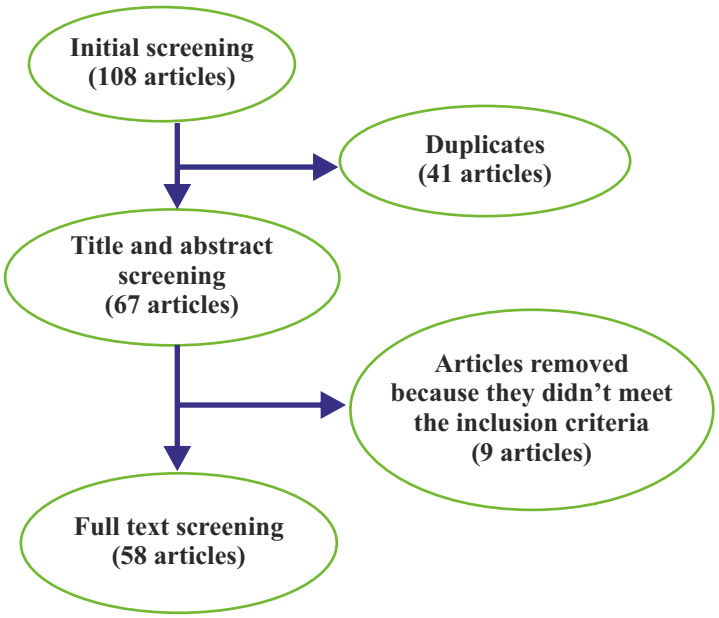

Figure 1: Flowchart of selection of articles

Results

Out of the initial 108 articles identified, 45 were ultimately included in the final review. The review revealed that regulatory T cells (Tregs) possess distinctive functional characteristics, such as balancing inflammation, regulating antigen-specific function, controlling immune response activation and function, and playing a critical role in defending against infections and managing autoimmune diseases. Furthermore, Tregs contribute to maintaining periodontal homeostasis by modulating periodontal inflammation, preventing soft tissue breakdown, and reducing alveolar bone resorption. Table 2 summarizes their role in periodontal disease.

Disscussion

Development of Tregs: Treg cells are heterogeneous with respect to their origin of development, functional activity, and activation (Figure 2). Tregs arise both in the thymus (tTregs) and extra thymically in the periphery (pTregs) as a through the induction of foxp3 upon exposure to antigens[14].

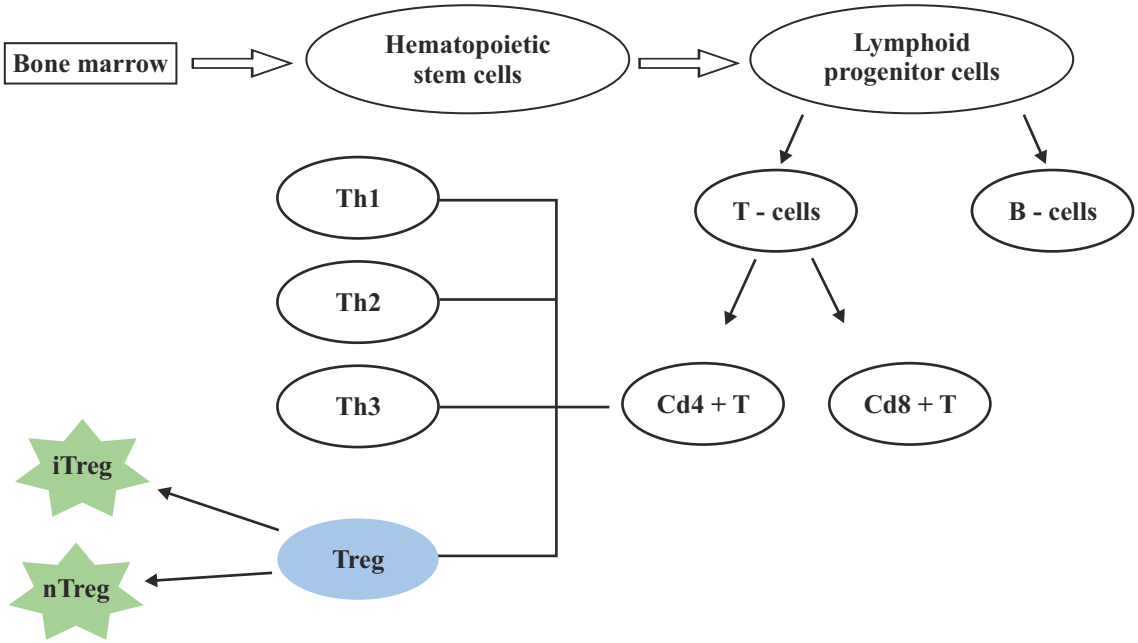

Figure 2: Development of T cells.
CD+4 – cluster of differentiation 4; CD+8 – a cluster of differentiation 4; Th- t- helper cells; Treg – T regulatory cells; iTreg- induced T regulatory cells; nTreg- natural -derived T regulatory cells;

Classification: Tregs are generally categorized into two groups:

- Thymus-derived Tregs (tTregs) or Natural-derived Tregs (nTregs)
- Peripherally derived Tregs (pTregs) or Induced Tregs (iTregs).

Two markers are used to differentiate nTregs versus iTregs, thereby maintaining immune homeostasis (Figure 3)[15]. Helios, a transcription factor from the Ikaros family (zinc finger protein/DNA binding protein), is significantly more abundant in nTregs compared to iTregs and is commonly used as a marker for Treg cells of thymic origin. Additionally, Neurophilin-1 (NRP-1 protein) is also abundant in nTregs[16].

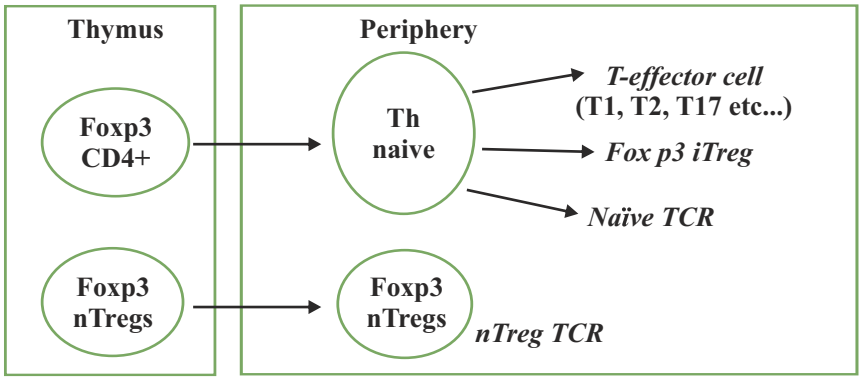

Figure 3: Thymic and Peripheral Generation of foxp3$^+$ Tregs Cells
Natural Treg (nTreg) cells differentiate in the thymus and migrate to peripheral tissues. Adaptive foxp3$^+$ Tregs (iTreg) cells differentiate in secondary lymphoid organs and tissues. The peripheral population of foxp3$^+$ Treg cells comprises both nTregs and iTregs cells. nTreg and Foxp3$^+$ iTregs cells differ in their TCR (T cell receptor) because iTregs cells are derived from mature peripheral naive CD4$^+$ cells.

Thymus-derived Tregs (tTregs) or Natural-derived Treg (nTreg)

Naturally occurring T-regulatory lymphocytes cells characterized by the expression of CD4+ and CD25+[17]. nTregs are the immunoregulatory elements that have an anergic phenotype and suppress exaggerated immune activity, thereby maintaining homeostasis[18]. nTregs cell development in the thymus involves several steps, which include intermediate interplay between self-reactive T-cell receptors (TCR) on developing thymocytes with corresponding pathogens showcased by specialized medullary thymic cells and hematopoietic antigen-presenting cells, results in the enhancement of foxp3 and other markers unique to Tregs cells[19]. The interaction

between TCR and self-antigens in the thymus is crucial for the differentiation of Tregs cells. Alongside TCR, co-stimulatory molecules contribute to Tregs cell differentiation, which includes OX40, tumor necrosis factor receptor 2 (TNFR2), CD28, and members of the tumor necrosis factor superfamily, which are Glucocorticoid-induced TNFR-related protein (GITR)[20]. Most of the intercellular signals are connected to the NF-κB pathway, the primary gene regulator in the thymic development of Tregs[21]. IL-2 upregulates foxp3 via CD25, which then signals for increased CD25 production, high expression of suppressor genes, and the delivery of regulatory functions in the final stage of differentiation[17].

Peripherally derived Treg (pTregs) or Induced Tregs (iTregs)

iTregs, characterized by CD25+, CD4+, and foxp3+ expression, are inhibitory cells crucial for maintaining immune balance and have the capability to inhibit T cell proliferation. Additionally, Treg differentiation from naive CD4+ T lymphocytes in the periphery is referred to as peripheral or induced Tregs (pTregs or iTregs). iTreg cells, located at mucosal interfaces, originated from mature CD4+ T cells extrathymically, thereby facilitating the tolerogenic antigen-presenting cells[22,23]. Although iTregs and nTregs cells serve similar functions, recent research emphasizes iTreg cells as a crucial and unique regulatory subset that augments nTreg cells, partly by enhancing TCR diversity within regulatory mechanisms[24]. Epigenetic distinctions have been noted between nTregs and iTregs cells, where nTregs have more stable foxp3 expression and wider demethylation. Various research and studies have shown the association between commensal microbiota and the development of iTreg cells[25]. Various signaling pathways impact the efficiency of inducible regulatory T-cell (iTreg) generation. Specific factors such as T cell receptor (TCR) affinity and related signals, along with co-stimulatory molecules and cytokines, play crucial roles in promoting optimal in vivo iTreg cell development[26]. iTregs cells are enriched at the environmental interfaces along with their specificities directed at microbial antigens[27]. A substantial portion of Tregs is found in peripheral tissues, particularly in tissues such as the lamina propria. Recently, iTregs have been shown to control autoimmune responses under certain inflammatory conditions[20].

Transcription factors of Tregs and their subsets

Tregs show immunosuppressive characteristics by the presence of CD25 and foxp3 (Figure 4). Additionally, other molecules such as amphiregulin, interleukin 10 (IL-10), cytotoxic T lymphocyte antigen-4 (CTLA-4), and transforming growth factor-beta 1 (TGF-β1)[28]. In 1995, Sakaguchi and colleagues showed that CD4+, CD25+ T cells could regulate autoimmune disease, highlighting the importance of the regulatory gene factor foxp3 as a specific marker of Treg cells. Foxp3, a key marker of Treg phenotype, plays a regulatory role in periodontal diseases. This transcription factor stabilizes the genetic profile of Tregs and controls their differentiation, maintenance, and suppressive functions[29]. In humans, not all cells expressing foxp3 are Tregs since foxp3 is highly enhanced in activated non-regulatory T cells, which indicates foxp3 is not a definitive regulatory marker for human Tregs. Some researchers propose that these non-Treg foxp3+ cells act as dormant Tregs, which can regain their regulatory function once activated[30,31]. Furthermore, since Foxp3 is a nuclear protein, it cannot be utilized to isolate viable Tregs. Consequently, various surface phenotypic markers have been identified to characterize Tregs and their subsets[32]. In humans, markers like CD25 and CD127 are used to isolate Tregs from peripheral blood and tissues[31]. Experimental studies indicate that a diminished presence of Tregs' phenotypic and functional markers, alongside impaired function, contributes to the advancement of human periapical lesions[32].

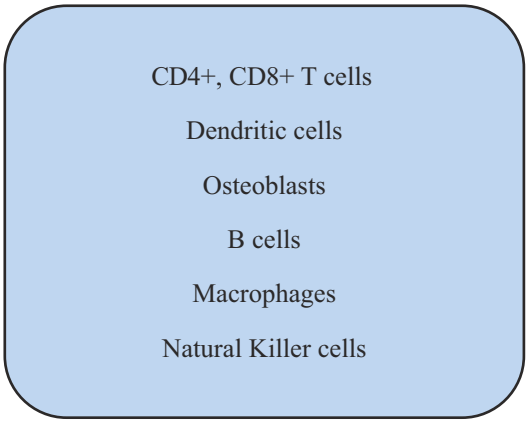

Figure 4 : Cellular targets of foxp3 Treg cell-mediated suppressor Functions

Nature of Tregs

1. **Plasticity retaining**

Plasticity is described as the ability to transform into other cell types, resulting in a change in function[33]. Under pathological conditions, physiological Tregs can transform into pathological Tregs, which are found in CD4+ T cell subsets, including Tregs and Th cells. Recent research indicates that Tregs maintain lineage plasticity, meaning they can convert into other T effector cell subsets under specific environmental conditions, such as prolonged inflammation or lymphopenia[34]. Danger signals, such as extracellular ATP or microbial stimuli, can prompt antigen-presenting cells

(APCs) to release cytokines like IL-1β. Tregs can suppress this response by using CD39 to hydrolyze extracellular ATP. Tregs can also be converted into pro-inflammatory IFN-γ-producing cells by IL-12, expressing TBX21 (T-box transcription factor) and CXCR3 (chemokine receptor-3), which loses suppressive capacity while retaining foxp3 expression (Th1 Treg)[35].

Table 1: Factors impacting Treg plasticity

T cell subsets	Type of Treg plasticity	Factors Influence
Th1-like	IFN-γ, IL-12	Infection or healthy conditions can lead to an increased expression of IFN-γ and TGF-beta in Tregs.[36]
	IL-27	Tregs with increased expression of TGF-beta and CXCR3 exhibit IL-10 secretion and maintain their suppressive function.[37]
	IL-4	Restraining IFN-γ expression in foxp3.[38]
	TGF-β, IL-2	Repressing differentiation from Tregs to Th1.
Th2-like	IL-4	Reprogramming of Th2-like cells.
	IL-5	Enhancing the promoting effect of IL-4.
Th17-like	IL-6, IL-21	Converting Tregs to inflammatory Th17 via activated STAT3.[39]
	IL-12, IL-23	Converting Tregs into inflammatory Th17.
	TGF-β, IL-2	Suppressing the conversion via decreased IL-6.
	IRF8, GATA3, IDO	Suppressing Tregs converting into Inflammatory Th17.[40]

Abbreviations: IL: Interleukin; *Th:* t helper cells; IFN-γ: interferon-gamma; TGF-beta: Transforming growth factor Beta; CXCR3: CXC chemokine receptor3; foxp3: forkhead box P3; Tregs: regulatory T cells; STAT: signal transducer and activator of transcription protein family; IRF: Interferon regulatory factors; GATA: GATA binding factor, IDO: Indoleamine 2,3-dioxygenase

1. **Suppressive characteristics**

Tregs primarily suppress the activation and proliferation of naive T cells, natural killer cells (NKs), natural killer T cells (NKTs), activated effector T cells, memory CD4+ T cells, CD8+ T cells, antigen-presenting cells (APCs), and B cells. Various potential mechanisms have been identified for the suppressive function of Tregs in the activation and proliferation of T effector cells, in vivo and in vitro[14].

These mechanisms can be classified into four distinct categories:

- Regulation of antigen-presenting cell maturation or function.
- Targeted cell death as a form of suppression.
- Metabolic disruption as a means of suppression.
- Inhibition through the use of suppressive cytokine

Mechanism of action of Tregs

Tregs act by down-regulating the activities of CD4+ and CD8+ effector T cells (Teff cells), natural killer (NK) cells, and antigen-presenting cells through the mechanism given below[19]. Treg cells are widely regarded as the primary mediators of peripheral immune tolerance.

Four modes of Suppressive action by Tregs are

1. Inhibition through inhibitory cytokines: IL-10 and TGF-β are crucial in down-regulating induced by Tregs cells, although they may not be necessary for Treg-cell function.

2. Suppression through cytolytic activity: The cytolytic activity of Treg cells involves granzyme A and perforin, which bind to CD18, leading to the down-regulation of B lymphocytes, Natural killer cell function, and cytotoxic T cells. Moreover, activated Treg cells can initiate apoptosis in effector T cells via pathways involving tumor necrosis factor-related apoptosis-inducing ligand-death receptor 5 (TRAIL-DR5)[41].

3. Suppression by metabolic disruption: Increased expression of CD25 by Treg cells is believed to consume IL-2; thus, Treg cells exert their suppressive effect through "metabolic disruption" on the target effector T cells.

4. Down-regulation by modulation of DC (Dendritic cell) maturation or function: Treg cells also modulate the immune response by interacting with dendritic cells, which play a critical role in activating effector T cells via the co-stimulatory receptor, cytotoxic T-lymphocyte antigen 4. Treg cells also stimulate DCs to produce indoleamine 2,3-dioxygenase (IDO), a potent regulatory molecule that generates proapoptotic metabolites through tryptophan breakdown, thereby suppressing T-cell proliferation. Additionally, Treg cells may regulate DCs' ability to activate effector T cells by reducing the expression of CD80 and CD86 molecules[42].

Role of Tregs and their involvement in developing periodontitis

The exact role of Treg cells in periodontitis is still disputed. While periodontopathogens are the main culprits behind periodontitis, the host's immune response ultimately determines the progression and clinical outcome of the disease. Foxp3 cells serve as a key regulator in controlling the immune response during infection[43]. CD4+ T cells can either enhance or suppress the host response by releasing cytokines and membrane molecules during the progression of periodontitis. A study demonstrated that increased frequency of Tregs plays a role in periodontal health maintenance. CD8+ T cells play a vital role in periodontal immune balance by producing IL-10 and TGF-β[44]. The increase in Tregs in periodontal tissue, along with heightened production of the anti-inflammatory IL-10 cytokine, suggests that Tregs play a protective role by modulating inflammatory responses to oral pathogens[45]. A disruption in Tregs cell regulation in periodontal disease may lead to greater periodontal tissue destruction. Also, Th17/Treg imbalance contributes to the progression of periodontal disease, even in the presence of local inflammation and long-standing dental plaque formation[46]. Various studies have reported the presence of enriched Tregs in infected periodontal tissues. Nakajima illustrated that Treg cells are seen in gingival connective tissues compared to those with gingivitis. Also, migration of CD4+ CD25+ T cells to gingival tissues affected by periodontitis relies on the expression of Chemokine ligand 17 (CCL17) and CCL22 Chemokine ligand 22 (CCL22) by the inflammatory cells, thereby attracting Tregs expressing Chemokine Receptor 4 (CCR4) or CCR8 Chemokine Receptor 8 (CCR8)[47]. Even though the quantity of Tregs rises during periodontitis, a portion of these cells may lose their ability to suppress. However, in inactive periodontal lesions, IL-10 mRNA expression was elevated. Tregs were lower in bone resorption lesions when compared to healthy gingival tissues in the presence of CD25+ and foxp3+, suggesting a potential transformation of Tregs into Th17 lymphocytes[48]. Thus, the functionality of Tregs is crucial to maintain a regulated immune response and prevent disease advancement or recurrence. The immunosuppressive mechanisms and tissue-repair functions of Tregs are essential for periodontal well-being[49]. Various therapeutic strategies have been explored to boost the population of Tregs in periodontal disease. One approach involves selectively attracting Tregs to specific diseased periodontal lesions using Microparticles releasing CCL22, which have effectively decreased bone resorption and increased the expression of markers associated with regeneration, osteogenesis, and anti-inflammatory activity in the periodontium of animal models[50].

Experimental studies in periodontitis

The role of Tregs and Th17 in the progression of periodontitis remains unclear. Thus, investigators investigated the ratio of Th17/Treg cells, as well as associated transcription factors and cytokines, in the peripheral blood, gingival tissues, and gingival crevicular fluid of rats at different stages of experimental periodontitis. The interventions aimed at increasing Treg activity during experimental periodontitis successfully halted alveolar bone resorption and showed that there was an increase in IL-10 and TGF-β1 production. Furthermore, foxp3+ cells, CD4+ CD25+, which are phenotypic markers of Tregs, were detected, enhancing immune homeostasis in periodontal destruction.

Table 2: Experimental studies are done - in vivo models (mice)

Author	Periodontitis model	Intervention	Results
Ashlee C. Greene et al., 2022.[58]	Induction of regulatory T cells locally in ligature-induced experimental periodontitis in mice	Combination of TGFβ, Rapamycin, and IL2 microspheres	Reduces alveolar bone loss, increases the local ratio of Tregs to T effector cells, and alters the local microenvironment's expression of inflammatory and regenerative markers.
Wang et al., 2015.[52]	Oral inoculation with *P. gingivalis*	Formalin killed *P. gingivalis*	Diminished alveolar resorption and inflammatory cell infiltrate in the periodontal lesion, shows the down-regulation of Th17 and up-regulation of Tregs.
Napimoga et al.., 2012.[53]	Oral inoculation with *A. Actinomycetocomitans*	15d- PGJ2 in PLGA nanocapsules	Inhibits periodontal loss by reducing the RANKL expression and lymphocyte infiltration.
Wang et al., 2014.[51]	Oral inoculation with *P. gingivalis*	Al- trans retinoic acid (ATRA)	ATRA inhibits periodontal bone resorption and the infiltration of inflammatory cells, leading to a decrease in the number of Th17 cells and down-regulation of IL-17 and RANKL. Additionally, ATRA increases the levels of CD4+, foxp3, and Tregs, while up-regulating IL-10 and TGF-beta 1.
Jin et al., 2014.[54]	Oral inoculation with *P. gingivalis*	Tamibarotene (Am80)	Am80 ameliorates periodontal bone loss, suppressing Th17 cytokines and enhancing Treg-related cytokines and up-regulation of IL- 10, TGF- beta 1 and foxp3.

Abbreviations: PGJ2: Prostaglandin J2; PLGA: poly (lactic- co- glycolic acid)

Immuno-modulation with Tregs in experimental studies with periodontitis

Reviewing studies indicated that periodontitis resolution occurs when alveolar bone loss is arrested, and inflammatory cell infiltration is decreased. Moreover, these findings showed a direct association with the synthesis of anti-inflammatory cytokines such as IL-10 and TGF-β1, coupled with a decrease in IL-17 levels[55].

1. Porphyromonas gingivalis-targeted vaccination

A study investigating the effects of vaccinating with killed *P. gingivalis* bacteria revealed a substantial decrease in alveolar bone resorption in the vaccinated group compared to the sham-vaccinated group[52].

1. Delivery of retinoic acid-based substances

All-trans retinoic acid (ATRA), an active metabolite of vitamin A, involved in maintaining a balance in immune responses.

Alveolar bone resorption

on inoculation with ATRA vaccination, there was a substantial and significant reduction in alveolar bone resorption in the test group[51]. Also, treatment with Tamibarotene (Am80), a synthetic retinoic acid receptor, resulted in decreased alveolar bone loss[54].Kim et al. prepared a novel epitope, Pep19, targeting human naive CD45RA+ Tregs to enhance the expression of Treg cells[56]. The highlights of the study indicated that Tregs, a subset of CD4+helper T cell with immune-modulating properties, are important in preserving peripheral tolerance, averting autoimmunity, and suppressing chronic inflammation. Tregs express transcription factors foxp3 and CD25. The suppressive functions of Tregs primarily involve regulating the activities of pro-inflammatory cells like T and B cells, neutrophils, and macrophages in the periodontal tissues. Tregs are crucial for maintaining periodontal health by managing inflammation, preventing soft tissue damage, and inhibiting alveolar bone resorption.

Limitations

Though there are many in-vitro studies eliciting the nature of the Tregs, there are insufficient human trials. An increased cost and risks associated with cell-based therapies may be the factors that impede progress with human trials[57].

Conclusion

This paper reviews the Tregs functional stability in periodontitis, which proves that in vivo experimental studies have succeeded in arresting alveolar bone resorption. Tregs protective function in periodontitis is mediated by anti-inflammatory cytokines, thereby reducing inflammatory sites. Human trials for inducing Tregs to treat periodontitis are uncommon, but various studies have reported such trials in other systemic diseases have been successful. More research is needed to imply this function in humans. To validate the effectiveness of therapeutic approaches for periodontitis, researchers must conduct further studies to enhance their understanding of the various subsets of Tregs, their adaptability, and their functions.

Conflict of Interest: Nil

Sources of funding: Nil

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Ethical consideration

In this study no human participants are involved. Since it's a review article, Ethics approval is not required.

Authors' Contribution

AA: Conceptualization, designing the study, definition of intellectual content, literature search, Manuscript preparation, editing, review; AS: Conceptualization, designing the study, definition of intellectual content, Manuscript preparation, editing, review; EK: Conceptualization; Manuscript editing, review; RI: literature search, Manuscript editing

Data availability statement

Data used for the present study is available in public domain.

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