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The Role of Distinct T Cell Subsets in Periodontitis—Studies from Humans and Rodent Models

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Abstract Periodontal disease results from an interaction between the host's defense mechanisms and the microorganisms that constitute the dental plaque biofilm, and penetrate gingival tissue. Therefore, the progression and severity of the disease are strongly modulated by the host immune response, particularly, T cell responses. Because T cells consist of a variety of subpopulations, numerous studies have attempted to associate an impaired balance between each T cell subset and periodontal tissue destruction in periodontitis patients. Here, we overview studies examining human specimens obtained from patients with periodontitis and experiments analyzing rodent models with age-related or pathogen-induced experimental periodontitis. Human research provides valuable insights but also inconsistent results, which may be attributed to the difference in experimental approaches and lack of evaluation of disease activity. Rodent models have shown that an optimal balance between functionally different T cells is essential in the protection against periodontal tissue destruction.

Keywords T cell · T cell subset · Periodontal disease · Periodontitis · Human specimen · Rodent model with periodontitis · $CD8^+$ cytotoxic T cell · $CD4^+$ helper T cell · Th1 · Th2 · Th17 · Regulatory T cell (Treg) · NKT cell

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Introduction

Periodontal disease results from an interaction between the host's defense mechanisms and the microorganisms that are present in dental plaque biofilms. Although bacteria play indispensable roles in the initiation of the disease, the subsequent progression and severity of the disease are strongly influenced by the host immune response. Periodontitis affects tooth-supporting bone and soft tissues and is a major cause of tooth loss. Periodontitis lesions are characterized as a predominant B cell response; however, T cells have an essential immunoregulatory role [1]. In addition, several studies have suggested the involvement of autoreactive T cells and autoantibodies in the pathogenesis of periodontitis [2–5].

Because it is well known that T cells are a heterogeneous population, and a balance between functionally different T cell subsets is crucial in immune regulation, a series of studies have attempted to associate an impaired balance between each T cell subset and periodontal disease progression. Nevertheless, it seems difficult to reveal this association because each T cell subset exhibits beneficial and detrimental properties depending on disease conditions [6].

In this review, we will discuss the presence and the role of various T cell subsets, including $CD8^+$ cytotoxic T cells, $CD4^+$ T helper cells (Th1, Th2, and Th17), regulatory T cells, and natural killer T (NKT) cells in the pathogenesis of periodontitis. To this end, we will give an overview of the human studies that analyzed specimens such as gingival tissues, gingival crevicular fluid, and peripheral blood obtained from periodontitis patients. In addition, we summarize the current knowledge about rodent models with age-related or

experimental periodontitis induced by major periodontopathic bacteria (Table 1).

$CD4^+$ Helper and $CD8^+$ Cytotoxic T Cell Lineages

$CD4^+$ and $CD8^+$ T cells differentiate from $CD4^+CD8^+$ double-positive precursors in the thymus and exhibit distinct antigen specificities and functions. $CD4^+$ T cells are major histocompatibility complex (MHC)-II-restricted and preprogrammed for helper functions, whereas $CD8^+$ T cells are MHC-I-restricted and preprogrammed for cytotoxic functions. Because the ratio of $CD4^+$ to $CD8^+$ T cells is one of the indexes to determine the character of immune responses, its association with periodontal disease progression has been extensively examined. Some researchers analyzed the cells extracted from human gingival tissues and found decreased CD4/CD8 ratios in periodontitis lesions compared with healthy sites or peripheral blood [23, 24]. According to histologic analysis, some studies reported decreased CD4/CD8 ratios in periodontitis lesions compared with gingivitis or healthy sites [25, 26], whereas some reported increased CD4/CD8 ratios [27, 28], and others found no differences in the ratios [29, 30]. As discussed below, contradictory results obtained in human studies could be attributable to differences in methodology between studies, and the timing of sampling relative to disease activity.

A few studies have examined the impact of $CD4^+$ and $CD8^+$ T cells on periodontopathic bacteria-induced alveolar bone resorption in mouse models. Baker et al showed that mice lacking MHC-II-restricted $CD4^+$ T cells, but not MHC-I-restricted $CD8^+$ T cells, were resistant to alveolar bone loss induced by *Porphyromonas gingivalis* oral infection [7]. In addition, oral *Aggregatibacter actinomycetemcomitans* challenge of NOD/SCID mice transplanted with peripheral blood lymphocytes from periodontitis patients (HuPBL-NOD/SCID mice) demonstrated that $CD4^+$ T cells, but not $CD8^+$ T cells, were essential mediators of alveolar bone destruction [8]. These findings in mouse models suggest that $CD4^+$ T cells contribute to bone destruction in periodontal disease.

$CD4^+$ T Helper Subsets (Th1, Th2, and Th17)

Several $CD4^+$ T cell subsets have been identified based on their distinct cytokine and transcription factor profiles [31]. Peptide affinity for MHC-II, T cell receptor activation, the expressed costimulatory molecules, and the cytokines secreted by dendritic cells collectively determine the signal strength that influences the differentiation of naïve T helper cells into Th1, Th2, Th17, or inducible regulatory T cells. Th1 and Th2 are classic T helper subsets that are characterized by the transcription factors T-bet and GATA-3, respectively. Th1 differentiation is accelerated by interleukin (IL)-12, while exposure to IL-4 drives Th2 differentiation. Th1 cells secrete IL-2 and interferon (IFN)-γ, which promote cell-mediated immunity by activating macrophages, $CD8^+$ T cells, and NK cells.

The Th1 response is essential in immune defense against intracellular bacteria, viruses, and tumors, but possibly promotes autoimmune disease. However, the Th2 response produces IL-4, IL-5, IL-6, IL-10, and IL-13, which mediate humoral immunity by promoting B cell proliferation, differentiation, and antibody production. The Th2 response is involved in parasitic worm immunity and allergic inflammatory responses, including airway hyper-reactivity. Th17 is a recently identified T helper subset that expresses the transcription factors RORγt and RORα and produces IL-17A, IL-17 F, IL-21, IL-22, and IL-26. It has been reported that cytokines such as IL-1β, IL-6, IL-21, IL-23, and TGF-β are important for Th17 differentiation and development.

Th17 cells play a protective role against extracellular bacteria and fungi but are also related to several autoimmune and inflammatory disorders such as the inflammatory bone destructive disorder rheumatoid arthritis [32]. Importantly, although Th1 and Th2 cells have inhibitory effects on osteoclastogenesis through IFN-γ and IL-4, respectively, Th17 is defined as an osteoclastogenic T helper subset because it induces receptor activator of nuclear factor-κB ligand (RANKL) on osteoclastogenesis-supporting cells such as osteoblasts and synovial fibroblasts. Additionally, IL-17 enhances local inflammation and increases the production of inflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-1, and IL-6, which further promote RANKL expression. Furthermore, Th17 cells themselves express RANKL and may participate directly in osteoclastogenesis [33, 34••].

Until the discovery of Th17, researchers had focused on the Th1/Th2 paradigm and attempted to identify either subset as causative for the progression of periodontal disease. In humans, numerous studies have supported the hypothesis that Th1 cells are associated with stable lesions and Th2 cells are associated with progressive lesions [35–40]. In contrast, several studies have demonstrated that upregulation of Th1 responses or downregulation of Th2 responses are involved in periodontal tissue destruction [41–43]. Moreover, others have shown a comparable presence of Th1 and Th2 cytokines in human periodontitis lesions [44–49].

To clarify the functional role of Th1 and Th2 in periodontal disease, several rodent models have been developed. Mice with *A. actinomycetemcomitans*-induced periodontitis demonstrated upregulation of Th1 cytokines (IFN-γ and IL-12) in the early stage and that of Th2 cytokines (IL-4 and IL-10) in the late stage, indicating the involvement of each T cell subset in different disease stages [9]. Destructive effects of Th1 and Th2 cytokines were suggested in an experiment that showed

Table 1 Association of T cells in rodent models with periodontitis

References	Pathogens	Animals	Summary
Baker et al [7]	P.g	SCID mice (lack of T and B cells), H2-Aβ KO mice (lack of MHC-II-restricted $CD4^+$ T cells), IFN-γ KO mice, and IL-6 KO mice	More resistant to ABL than WT mice
		Beta-2 microglobulin KO mice (lack of MHC-I-restricted $CD8^+$ T cells)	Similar susceptibility to WT mice
Teng et al [8]	A.a	HuPBL-NOD/SCID mice, and those depleted of $CD8^+$ T cells	More susceptible to ABL than NOD/SCID mice
		HuPBL-NOD/SCID mice depleted of $CD4^+$ T cells	Similar susceptibility to ABL to NOD/SCID mice
		Naïve NOD/SCID mice adoptively transferred with $CD4^+$ T cells from A.a-inoculated HuPBL-NOD/SCID mice	More susceptible to ABL than NOD/SCID mice via RANKL expression on $CD4^+$ T cells
Garlet et al [9]	A.a	Mice	Th1 response in early stage; Th2 response in late stage
Teng et al [10]	A.a	HuPBL-NOD/SCID mice	ABL accompanied by Th1 response; pathogenicity of IFN-γ
Kawai et al [11]	*1	Rats transferred with antigen-specific Th1 clone cells	More susceptible to ABL than mice without T cell transfer
		Rats transferred with antigen-specific Th2 clone cells	Similar susceptibility to ABL to mice without T cell transfer
		Rats administrated with CTLA4Ig followed by transfer of Th1 clone cells	More resistant to ABL than rats without administration of CTLA4Ig
Myneni et al [12]	T.f	Mice	ABL accompanied by Th2 response
Liu et al [13]	P.g	Mice immunized with P.g-derived antigen plus CpG oligodeoxynucleotides	Protective against ABL; association of both Th1 and Th2 responses
Alayan et al [14]	*2	IFN-γ KO, IL-12p40 KO, IL-4 KO, and IL-10 KO mice	More susceptible to age-related ABL than WT mice
Yu et al [15]	P.g	IL-17RA KO mice	More susceptible to ABL due to deficits in neutrophil migration
de Brito Bezerra et al [16]	A.a	Rats	ABL accompanied by increase of $CD8^+$ cells and no change of $CD4^+$ or $Foxp3^+$ cells.
Garlet et al [17]	A.a	Mice with Treg inhibition by injection of anti-GITR monoclonal antibodies	Further enhanced ABL; decreased CTLA-4, IL-10, and TGF-β; increased IFN-γ and RANKL
Wang et al [18•]	P.g	Mice with oral administration of all-trans retinoic acid	Reduced ABL accompanied by reduced Th17 and increased Treg response
Glowacki et al [19•]	A.a or P.g	Mice with gingival injection of CCL22-releasing microparticles	Reduced ABL; increased Treg-associated molecules; decreased proinflammatory cytokines
Sasaki et al [20]	P.g	IL-10 KO mice	More susceptible to ABL than WT mice
Zhang et al [21]	A.a	HuPBL-NOD/SCID mice intraperitoneally injected with IL-10	Reduced ABL associated with decreased Th1 response
Aoki-Nonaka Y et al [22••]	P.g	CD1d KO mice (lack of Vα14 NKT cells)	More resistant to ABL than WT mice
		Mice injected with α-galactosylceramide (activation of NKT cells)	More susceptible to ABL than control mice

Periodontopathic pathogens were orally administrated unless otherwise noted. *1, A.a 29-kDa outer membrane protein and LPS were injected into gingiva. *2, No pathogen was used

A.a *Aggregatibacter actinomycetemcomitans*, ABL alveolar bone loss, P.g *Porphyromonas gingivalis*, SCID severe combined immunodeficiency, T.f *Tannerella forsythia*

that IFN-γ- and IL-6-deficient mice were resistant to *P. gingivalis*-induced alveolar bone loss [7]. However, the pathogenic role of Th1 cells, as opposed to Th2 cells, was indicated in a study using HuPBL-NOD/SCID mice with *A. actinomycetemcomitans*-induced alveolar bone resorption, in which bone loss was associated with $CD4^+$ T cells expressing IFN-γ rather than IL-4. In addition, the injection of IFN-γ into the mice further enhanced the bone loss [10]. Furthermore, adoptive transfer of antigen-specific Th1 cells but not Th2 cells enhanced alveolar bone destruction in rats injected with the *A. actinomycetemcomitans* 29-kDa outer membrane protein and lipopolysaccharide (LPS) into gingiva [11]. In contrast, a pathogenic role of the Th2 response was proposed in a study demonstrating that *Tannerella forsythia*–induced alveolar bone loss was accompanied by an increase in IL-5 but not of IFN-γ or IL-17 [12]. However, the protective roles of the Th1 and Th2 subsets were suggested in several articles, as described below. Oral gavage of *P. gingivalis*-derived antigen plus CpG oligodeoxynucleotides decreased their susceptibility to *P. gingivalis*-induced alveolar bone destruction, which was accompanied by upregulated production of Th1 and Th2 cytokines such as IFN-γ, IL-4, IL-5, and IL-6 in antigen-specific $CD4^+$ T cells [13]. In addition, deficiency in the individual Th1 or Th2 cytokines (IFN-γ, IL-12p40, IL-4, or IL-10) resulted in enhanced, age-related alveolar bone loss [14].

It has become apparent that the pathogenesis of periodontitis cannot be fully explained through the prism of the Th1/Th2 paradigm; therefore, the discovery of Th17 has been expected to clarify the complex pathogenesis of periodontitis. Numerous reports have shown an elevated level of IL-17 in gingival tissues or gingival crevicular fluid from periodontitis lesions compared with healthy sites [50–57]. These reports also demonstrated the association of other Th17-related cytokines (eg, IL-1β, IL-6, IL-21, and IL-23) with periodontitis. In addition, immunohistochemical analysis revealed an increased infiltration of $IL\text{-}17^+$ cells or $RORC2^+$ (human homologue of mouse RORγt) cells in periodontal lesions [58••, 59, 60]. Furthermore, the serum concentration of IL-17 was dramatically increased in aggressive periodontitis patients compared with healthy subjects [61]. Zhao et al reported that nonsurgical periodontal therapy reduced the proportion of $IL\text{-}17^+$ cells in peripheral blood $CD4^+$ T cells. The authors also demonstrated decreased IL-17, increased IL-4, and no change in IFN-γ levels in gingival crevicular fluid after treatment [62•]. However, the question arises as to whether the increased Th17 cells are protective or destructive in periodontal diseases.

The protective role of Th17 cells against periodontal tissue destruction was suggested by a study using mice deficient for IL-17RA, a member of the IL-17 receptor family. The mice were susceptible to *P. gingivalis*-induced alveolar bone loss because of deficits in neutrophil migration [15]. However, mice lacking functional IL-17 or IL-23 are resistant to joint bone erosion induced by collagen-induced arthritis, which implies a destructive aspect of Th17 cells [63, 64]. The apparent difference in these studies may be due to the importance of Th17 cells in the control of infection (eg, periodontitis), but not in noninfectious diseases (eg, autoimmune arthritis).

Collectively, human and animal studies suggest that each T-helper subset possibly has beneficial and detrimental aspects in the pathogenesis of periodontal disease; thereby, an appropriate balance between the functionally different subsets may be important to eliminate infection and abrogate tissue destruction. The precise role of Th17 cells in physiological and pathologic conditions, including actions on innate immunity and osteoclastogenesis, should be further explored because Th17 cells and their cytokines are consistently increased in human periodontitis lesions.

Regulatory T Cells

Immunological self-tolerance is supported by several mechanisms: physical elimination (clonal deletion), functional inactivation (anergy), and T cell-mediated suppression. Regulatory T cells, which suppress the activation, proliferation, and effector functions of a wide range of immune cells, play a crucial role in maintaining immune homeostasis and in regulating immune responses in inflammatory conditions [65]. To date, several types of regulatory T cells have been described and have 2 main subsets: naturally occurring $Foxp3^+$ Tregs, which develop in the thymus, and inducible regulatory T cells (eg, IL-10-producing Tr1 cells, TGF-β-producing cells, inducible $Foxp3^+$ regulatory T cells), which develop in the periphery after exposure to various signals. $Foxp3^+$ Tregs constitutively express CD25 at a high level and other Treg-related molecules, such as CTLA-4, GITR, CD122, CD44, CD11a, and CD54. Mutation of the Foxp3 gene elicits fatal autoimmune and inflammatory diseases due to the lack of functional Tregs [66, 67]. Multiple mechanisms of $Foxp3^+$ Treg-mediated suppression have been suggested: impairment of dendritic cell function to activate effector T cells, a CTLA-4-dependent mechanism, anti-inflammatory cytokines (eg, IL-10 and TGF-β), and other mechanisms. Intriguingly, Tregs also regulate bone metabolism by directly inhibiting osteoclastogenesis, which is most likely mediated by Treg-derived cytokines such as TGF-β, IL-10, and IL-4, or CTLA-4 [20].

Therefore, $Foxp3^+$ Tregs are suggested to play an essential role in the regulation of inflammation in periodontitis lesions where various types of effector/self-reactive T cells infiltrate. In humans, several reports have demonstrated increased infiltration of Tregs in lesions. The proportion of $CD4^+CD25^+$ T cells in lymphocytes extracted from gingival tissues was higher than that from peripheral blood in periodontitis patients

[68], and Foxp3 gene expression was upregulated in periodontitis lesions compared with gingivitis lesions/healthy sites [69, 70]. In accordance with these findings, immunohistologic analysis showed an increased infiltration of $CD4^+CD25^+$ T cells and $Foxp3^+$ cells in periodontitis lesions [58••, 59, 69, 71]. In addition, $CD4^+CD25^+$ T cells extracted from periodontitis lesions expressed Treg-related molecules such as Foxp3, CTLA-4, and GITR at a high rate [70]. Inconsistent with the many studies described above, Ernst et al reported that $Foxp3^+CD25^+$ cells were reduced in periodontitis lesions [72]. However, the reason for the discrepancy has not been clarified.

In rats, *A. actinomycetemcomitans*-induced experimental periodontitis did not change the proportion of $Foxp3^+$ cells in draining node lymphocytes [16]. In contrast, mice with *A. actinomycetemcomitans*-induced alveolar bone loss showed an increased number of $Foxp3^+CD4^+$ T cells and elevated expression of CTLA-4, IL-10, and TGF-β in gingival tissues [17]. It is noteworthy that this study also showed that the inhibition of Tregs by anti-GITR treatment downregulated the Treg-related molecules, but upregulated IFN-γ and RANKL, and further enhanced bone loss without changing the bacterial load. These data indicate the possibility that Tregs attenuate the severity of periodontitis without impairing infection control. More recent research demonstrated that all-trans retinoic acid (ATRA) suppressed *P. gingivalis*-induced alveolar bone loss and inflammatory cell infiltration, which was accompanied by an increase of $Foxp3^+$ cells and the level of IL-10 and TGF-β, and a decrease of $ROR\gamma t^+$ cells and the level of IL-17 [18•]. In addition, the suppressive effect of $Foxp3^+$ Tregs on inflammation-mediated bone loss was elegantly demonstrated in the latest literature. Glowacki et al reported that recruitment of $Foxp3^+$ Tregs into gingival tissue by injection of C-C motif chemokine ligand 22 (CCL22)-releasing microparticles induced an increase of Treg-associated anti-inflammatory molecules, a decrease of proinflammatory cytokines, and a marked reduction of alveolar bone resorption in mice with *A. actinomycetemcomitans*-induced experimental periodontitis [19•]. These findings suggest that ATRA-induced or CCL22-mediated immune modulations may be novel therapeutic approaches to control periodontitis.

CTLA-4-mediated suppression is considered to be a central mechanism of $Foxp3^+$ Treg function [73]. Immunohistologic analysis showed only a small number of $CTLA\text{-}4^+$ cells in periodontitis lesions and healthy sites [74, 75]. In rats, administration of CTLA4-immunoglobulin fusion proteins (CTLA4Ig) abrogated the alveolar bone resorption that was induced by gingival injection of *A. actinomycetemcomitans*-derived antigens, suggesting a protective role of CTLA-4 in periodontitis [11]. Anti-inflammatory cytokines are an additional mechanism through which regulatory T cells control inflammation. IL-10 is produced by various cell populations, including regulatory T cells and T-helper subsets. IL-10 gene expression was higher in periodontitis tissues than in healthy sites or peripheral blood mononuclear cells [70, 76]. In addition, $IL\text{-}10^+$ cells were widely distributed in periodontitis lesions [77]. The protective role of IL-10 was suggested by studies where IL-10-deficient mice displayed increased susceptibility to age-related or *P. gingivalis*-induced alveolar bone loss [14, 20]. The intraperitoneal injection of IL-10 into *A. actinomycetemcomitans*-infected HuPBL-NOD/SCID mice suppressed alveolar bone loss, which further supported the protective role of IL-10 [21]. TGF-β is another immunosuppressive cytokine with pleiotropic functions. Like IL-10, several reports show that TGF-β gene expression and $TGF\text{-}\beta^+$ cells were increased in human periodontitis lesions [69, 70, 78]. However, Dutzan et al showed a negative correlation between the levels of IL-10 and TGF-β and the presence or disease activity of periodontitis in humans [57, 79]. Taken together, a large number of studies support the view that regulatory T cells are recruited into periodontitis lesions and protect against tissue destruction; therefore, impairment of their function may be linked to the progression of periodontal disease.

Interestingly, nearly all $CD4^+$ T cell clones that were established from periodontitis tissues expressed the Foxp3 gene, and the $Foxp3^+CD4^+$ T cell clones did not exhibit a suppressive function in vitro [80, 81]. Although it is possible that the T cell clones were derived from non-Tregs that could express transient Foxp3 after activation [82], a fraction of $Foxp3^+$ T cells in periodontitis lesions might be functionally impaired. Recent studies have shown that appropriate stimuli convert human $Foxp3^+$ Tregs into IL-17-producing cells in the presence of IL-2 and inflammatory cytokines in vitro [83–85]. Indeed, $IL\text{-}17A^+Foxp3^+$ cells seem to be involved in periodontitis and other disorders such as psoriasis, inflammatory bowel disease, and colon cancer, although their roles are not fully elucidated [58••, 86–88].

NKT Cells

Invariant NKT (iNKT) cells are characterized by the coexpression of the natural killer cell receptor, NK1.1 (CD161), and restricted T cell receptors, Vα24Jα18 in humans and Vα14Jα18 in mice. Multiple iNKT cell populations differ in their function, location, and phenotype. iNKT cells typically recognize glycolipids that are presented by CD1d molecules, which are predominantly expressed on antigen-presenting cells (eg, dendritic cells, macrophages, and B cells) [89]. It has been reported that iNKT cells recognize antigens derived from bacteria such as *Borrelia burgdorferi*, *Sphingomonas* spp, *Streptococcus pneumonia*, and group B streptococcus [90–92]. In addition, some self-antigens are proposed to contribute to iNKT cell function [93]. iNKT cells rapidly respond to antigens and release substantial amounts of IFN-γ and IL-4, which subsequently activate other

lymphocytes and shape the course of adaptive responses. Thus, iNKT cells play important functions in autoimmune disease, cancer, infection, and inflammation [94]

Several studies have reported the involvement of iNKT and $CD1d^+$ cells in human periodontitis. Yamazaki et al used single-strand conformation polymorphism analysis to demonstrate that the proportion of NKT cells was elevated in periodontitis lesions compared with gingivitis lesions [95]. Immunohistologic analysis revealed that $CD1d^+$ and iNKT cells were increased in periodontitis lesions, and a fraction of the $CD1d^+$ cells was identified as $CD19^+$ B cells [96]. A more recent report showed increased iNKT cells in gingival tissues with aggressive periodontitis, but not chronic periodontitis, compared with healthy biopsies [97].

The pathogenic role of NKT cells in periodontal bone destruction was suggested by experiments utilizing mice with either a deficiency or activation of NKT cells. $CD1d^{-/-}$ mice, which lack Vα14 NKT cells, were completely resistant to *P. gingivalis*-induced alveolar bone resorption. In contrast, administration of α-galactosylceramide, which activates NKT cells in a CD1d-dependent manner, further accelerated *P. gingivalis*-induced bone resorption [22••]. However, it is still unknown whether *P. gingivalis*-derived antigens were directly recognized by NKT cells in the mouse models. To apply the pathogenicity of NKT cells in mice to humans, it should be determined whether the NKT cells observed in human periodontitis lesions are sufficiently activated to skew immune responses.

Conclusions

It is clear that T cells in periodontal tissues play a crucial role in infection control and tissue destruction in periodontal disease, whereas the mechanism of immune regulation underlying the disease is highly complicated. In humans, numerous studies have revealed phenomena that occur in periodontitis lesions by using a variety of materials and methods. These studies provide valuable insights into the T cell-mediated immune regulation of the pathogenesis of periodontitis, but they have also shown inconsistent results, which may be attributed to differences in the experimental approaches and a lack of evaluation of disease activity. Because it is considered that a diseased site exhibits an active state at times, but

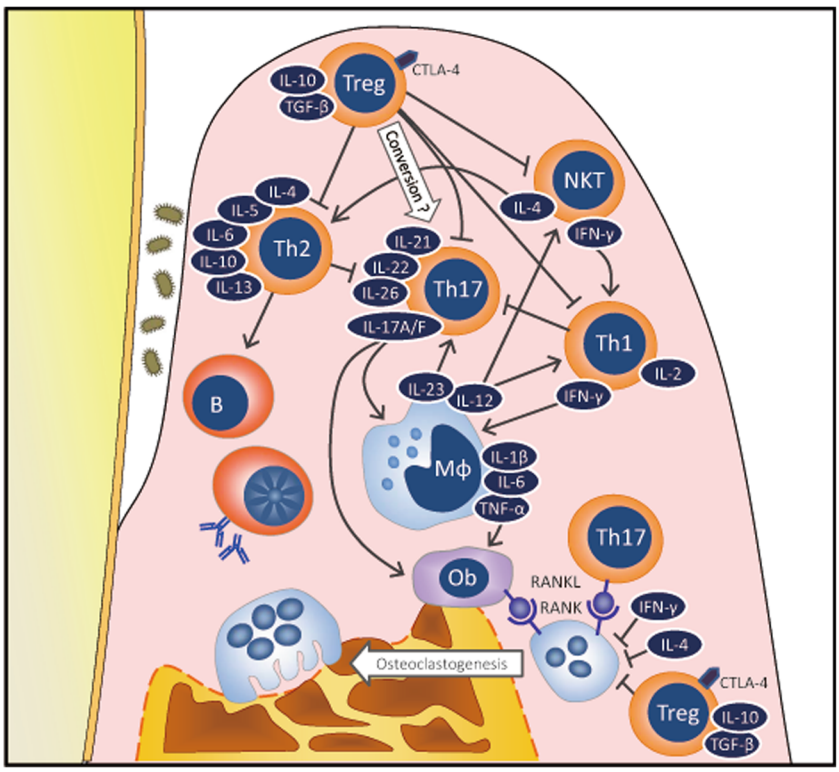

Fig. 1 The potential role of distinct T cell subsets in inflammatory responses and alveolar bone resorption in periodontitis lesions. As a consequence of sustained infection by periodontopathic bacteria, an adaptive immune response is established. NKT cells are involved in shaping the course of the immune response. Th1, Th2, and Th17 cells contribute to infection control in different ways because of their distinct cytokine profiles. However, their action also enhances inflammatory responses that lead to periodontal tissue destruction. Particularly, Th17 cells have a high potential to facilitate osteoclastogenesis thorough the production of IL-17 to induce RANKL expression on osteoblasts, enhancement of local inflammation, and RANKL expression on themselves. However, Tregs attenuate the inflammatory responses by suppressing other immune cells and inhibit osteoclastogenesis; therefore, they could protect against tissue destruction. Enhanced inflammation may convert a fraction of Tregs to IL-17-producing cells. Mϕ macrophage, Ob osteoblast

inactive state at other times, the change of disease activity could affect the immune responses at local sampling sites. What is not addressed in clinical studies because of ethical considerations can possibly be examined in research with animal models.

Several studies on experimental periodontitis in mice with deletions of T cell-related genes have implicated that an optimal balance between functionally different T cells may be more important in the protection against periodontal tissue destruction than a strong, polarized response on either side. This framework could be applied to humans, although it should be noted that these periodontitis models do not represent all aspects of human periodontal disease. Gemmell et al proposed that T cells are homeostatic in maintaining a balance between the host and biofilm, and disease progression occurs if the homeostatic balance is disrupted by environmental influences that lead to increased pathogens or depression of the host's defense mechanisms [1].

Finally, we briefly summarize the potential role of T cells in inflammatory responses and bone destruction in Fig. 1, where the T cells form a cytokine network that affects other immune and resident cells. Current approaches in periodontal treatment include the removal of bacteria and their components rather than modulating the host response. However, a deeper understanding of how T cells regulate the balance between protective and destructive immune responses may contribute to the development of new therapeutic modalities for periodontal disease in the future.

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Compliance with Ethics Guidelines

Conflict of Interest Dr. Takafumi Okui, Dr. Yukari Aoki-Nonaka, Dr. Takako Nakajima, and Dr. Kazuhisa Yamazaki each declare no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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