ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

Research Progress on the Immune Response of Peri-implantitis

Jingyi Yuan[1,2,a], Xiaorui Geng[1,2,b,*]

[1]Key Laboratory of Oral Disease Research (Guizhou Provincial Department of Education & Zunyi City), School of Stomatology, Zunyi Medical University, No. 1, Campus St., Xinpu Dist., Zunyi, 563000, China
[2]Shenzhen Key Laboratory of Otolaryngology, Shenzhen Institute of Otolaryngology, Shenzhen Longgang Otolaryngology Hospital, Shenzhen, 518172, Guangdong Province, China
[a]jingyiy818@163.com, [b]gengxr0716@163.com
[*]Corresponding author

Abstract: *The pathogenesis of peri-implantitis originates from an immune-inflammatory response provoked by microbial dysbiosis, with clinical manifestations including advancing peri-implant mucosal inflammation and progressive bone resorption. Although its outward presentation may resemble that of periodontitis, tissue destruction in peri-implantitis tends to be more accelerated and extensive, due to the unique anatomical structure and distinct immune microenvironment surrounding implants. Immune dysregulation is pivotal in the disease process, influencing the balance among immune cell subsets, the production of inflammatory cytokines, and the activation of key molecular signaling pathways. This review systematically synthesizes recent advances, highlighting that peri-implantitis exhibits a distinct and often more intense inflammatory profile than periodontitis, and that an imbalance in macrophage M1/M2 polarization along with T-cell subset dysregulation serve as critical drivers of tissue destruction. By consolidating current evidence, the article aims to provide a comprehensive perspective on the immunopathological mechanisms of peri-implantitis and to establish a theoretical foundation for the development of precision immunotherapy.*

Keywords: *Peri-implantitis; Immune dysregulation; Macrophage polarization; T-cell subsets*

1. Introduction

Peri-implantitis is an inflammatory condition closely associated with plaque accumulation that affects the tissues surrounding dental implants, featuring ongoing inflammation of the peri-implant mucosa accompanied by a gradual loss of the supporting alveolar bone. When the disease progresses to an advanced stage, it may ultimately result in implant loss [1, 2]. In recent years, the rising popularity of implant procedures has been accompanied by a higher prevalent of peri-implantitis. According to the latest systematic reviews and meta-analyses, at the patient level, the prevalence of peri-implant mucositis is approximately 46%, whereas peri-implantitis affects as many as 21% of individuals; notably, this figure is even greater among patients who do not attend regular maintenance visits [3].

Evidence from animal studies and human biopsy analyses indicates that peri-implantitis is associated with more rapid and extensive tissue destruction than periodontitis, with inflammatory infiltrates extending more directly toward the bone crest [2, 4]. This difference is primarily explained by the peri-implant region lacking the periodontal ligament and its embedded Sharpey's fibers. The connective tissue fibers here run mostly parallel to the implant surface, creating only a relatively weak soft tissue seal [5]. Such anatomical limitation compromises the barrier against bacterial challenge, forming the structural basis for the distinct immune response observed around implants.

In peri-implantitis, immune dysregulation emerges as a key factor in the pathological process, affecting the equilibrium among immune cell subsets, the release of inflammatory mediators, and the initiation of critical intracellular signaling pathways [6]. The host response to microbial biofilms around implants depends on a coordinated interplay between innate and adaptive immunity. Innate immune cells—including neutrophils, macrophages, and dendritic cells—serve as the first line of defense through rapid but non-specific mechanisms, while T and B lymphocytes mediate antigen-specific recognition and long-term immunological memory [7-9]. In the context of peri-implantitis, however, this fine-tuned balance can become disrupted, tilting the balance from host defense toward tissue

ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

destruction and thereby promoting the characteristic alveolar bone resorption.

This review systematically summarizes recent advances in our understanding of immune responses in peri-implantitis, highlighting that peri-implantitis elicits distinct immunological features compared to periodontitis. We focus on the dual roles of innate immune cells—particularly neutrophils and macrophages—in both host defense and tissue destruction, and examine the complex dynamics of adaptive immunity involving T-cell subsets and B-cell responses. By integrating current evidence from human studies, animal models, and transcriptomic analyses, this article aims to provide a comprehensive perspective on the immunopathological mechanisms of peri-implantitis and to establish a theoretical foundation for the development of precision immunotherapy approaches.

2. Innate Immune Dysregulation in Peri-Implantitis

As the first line of host defense against microbial dysbiosis and foreign body stimulation, the innate immune system plays an irreplaceable and pivotal role in the initiation, progression, and persistence of peri-implantitis. Unlike adaptive immunity, which necessitates antigen presentation and clonal expansion, the innate immune system elicits a rapid response to microenvironmental perturbations in the peri-implant region, via a sophisticated network of immune cells, inflammatory cytokines and signaling pathways that collectively orchestrate the balance between tissue protection and destructive inflammation. Specifically, innate immune responses are initiated through the recognition of pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and other inflammatory cues by pattern-recognition receptors [10, 11]. Neutrophils, macrophages, and dendritic cells are the key cellular effectors of this innate immune response [12]; these cells drive inflammation by phagocytosing pathogenic bacteria and releasing various mediators, including cytokines, matrix metalloproteinases (e.g., MMP-8), and chemokines [13].

2.1 Neutrophils: Early Responders and Amplifiers of Tissue Destruction

Neutrophils act as the host's first line of defense against pathogenic invasion and exert a dual role in the immunopathological process of peri-implantitis, serving as both critical early defenders and prominent amplifiers of subsequent tissue destruction. In peri-implantitis lesions, neutrophils exhibit a marked increase in quantity and hyperfunction, with their excessive and dysregulated responses constituting the core mechanism of persistent inflammation and tissue destruction [14, 15]. As the primary innate immune cells in healthy gingiva, both functional deficiency and excessive activation of neutrophils can lead to damage of periodontal tissues [16, 17]. Evidence from a murine model of peri-implantitis reveals a pronounced neutrophilic response, characterized by significantly elevated neutrophil percentages and densities, indicating a more aggressive and dysregulated host immune response compared to periodontitis [18].

Microorganisms and their products (e.g., lipopolysaccharides) accumulate in the peri-implant pocket, triggering the production of large amounts of chemokines in local tissues, which drive the rapid recruitment of neutrophils from the circulatory system to the lesion site [19]. Single-cell RNA sequencing analysis revealed the existence of a unique pro-inflammatory $CXCL13^{+}$ fibroblast subpopulation in the peri-implantitis microenvironment, which specifically and abundantly recruits neutrophils via the CXCR2/CXCR1 receptor axis through the secretion of CXCL8 (IL-8) and CXCL6 [14]. Clinical studies further confirm that, compared to healthy implant tissues, the gene and protein expression levels of CXCL8 and CXCL5 in peri-implantitis soft tissues are significantly upregulated. These chemokines are associated with enhanced neutrophilic inflammation, potentially through PI3K/Akt/NF-κB-related signaling [20].

Activated neutrophils eliminate microorganisms through phagocytosis, phagolysosome formation, activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), and the release of reactive oxygen species (ROS) and proteases. However, these effector mechanisms, while essential for host defense, can also inflict significant collateral damage on surrounding host tissues [15]. Upon activation, neutrophils degranulate and release substantial quantities of proteolytic enzymes stored within their granules, including matrix metalloproteinase-8 (MMP-8). Clinical studies have demonstrated that levels of active MMP-8 in peri-implant sulcular fluid (PISF) are significantly elevated at diseased sites compared to healthy controls. The active form of MMP-8 directly degrades extracellular matrix components, particularly collagen, thereby disrupting the integrity of soft tissue attachment around implants [21]. Concurrently, the activated NADPH oxidase complex generates large amounts of ROS, which not only exert microbicidal effects but also induce oxidative damage to

ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

adjacent tissues, further amplifying local inflammatory signals [15]. Beyond their role in soft tissue destruction, neutrophils may also contribute to bone resorption through RANKL-dependent mechanisms, as activated neutrophils have been shown to express membrane-bound RANKL in inflammatory settings [15, 22].

2.2 Macrophages: A Double-Edged Sword in Functional Polarization

As central effector cells of the innate immune system, macrophages maintain the host-microbe equilibrium, participate in antigen presentation, mobilize multiple host defense mechanisms and mediate resistance to bacterial challenges. Their remarkable plasticity allows them to adopt distinct functional states that exert a profound influence on the course of inflammation and the delicate balance between tissue breakdown and subsequent repair [23, 24]. In response to cues present in the local milieu, macrophages undergo polarization toward different phenotypes, most notably the classically activated M1 and the alternatively activated M2 subtypes [25]. M1 macrophages, the prototypical proinflammatory phenotype, are typically induced by exposure to lipopolysaccharide (LPS) or interferon-γ (IFN-γ). They are characterized by the upregulated expression of inducible nitric oxide synthase (iNOS), CD86 and CD80, along with the abundant secretion of proinflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-12 (IL-12). Through these mediators, M1 macrophages initiate and propagate inflammatory responses while exhibiting potent antimicrobial and antitumor activities [26, 27]. In contrast, M2 macrophages, which exert anti-inflammatory and pro-reparative effects, are induced by cytokines such as interleukin-4 (IL-4) and interleukin-13 (IL-13). They display high expression levels of CD206 and arginase 1 (Arg1), and secrete factors including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) that promote the resolution of inflammation, facilitate tissue repair, induce angiogenesis and drive fibrotic processes [26, 27]. A disruption of the M1/M2 balance, with a shift toward M1 macrophage dominance, is a hallmark feature of numerous chronic inflammatory conditions.

In recent years, multiple studies have revealed unique patterns of macrophage polarization through the analysis of human peri-implantitis tissue samples. Although early research was controversial, recent evidence tends to be consistent: the number of macrophages in peri-implantitis lesions is significantly increased, predominantly with M1-type polarization [28, 29]. Compared with periodontitis, the proportion and density of M1-type macrophages ($iNOS^+$ or $CD80^+$) in peri-implantitis tissues were significantly higher, while the proportion of M2-type macrophages ($CD206^+$) showed no significant difference or was relatively lower, resulting in an increased M1/M2 ratio [28-30]. Notably, in cases of severe peri-implantitis (advanced bone resorption), the expression of M1 macrophages was significantly higher than that of M2 macrophages, and the proportion of M1 macrophages showed a positive correlation with the probing depth [29]. These findings suggest that excessive polarization of M1 macrophages and the M1/M2 imbalance are key factors driving the persistent progression of peri-implantitis and bone destruction. Transcriptomic analysis also confirmed that, compared to periodontitis, peri-implantitis exhibits more pronounced macrophage activation and bone loss [31].

The distinctive environment around dental implants delivers intricate cues that guide macrophage behavior. Within the plaque biofilm, molecular motifs derived from pathogens—most notably LPS derived from Gram-negative species—engage Toll-like receptors (TLRs) on macrophages, thereby triggering their activation and driving them toward an M1 phenotype. This shift is accompanied by the abundant secretion of pro-inflammatory mediators [23, 32]. Additionally, particles and ions shed from implant surfaces through wear or corrosion processes function as either foreign materials or DAMPs. Upon phagocytosis by macrophages, these elements stimulate the NLRP3 inflammasome, facilitating the maturation and release of IL-1β while also reinforcing M1 polarization [33-36]. Work by Eger and colleagues (2018) substantiates this, showing that exposure to titanium particles elicits a pronounced M1 shift, accompanied by elevated release of IL-1β, IL-6, and TNF-α [34]. More recently, Carrillo-Galvez and coworkers (2025) uncovered a synergistic interaction: LPS combined with titanium ions activates the NLRP3 inflammasome through pathways dependent on reactive oxygen species, while also indirectly engaging the AIM2 inflammasome, thereby amplifying the overall inflammatory cascade [37].

Polarized macrophages regulate the balance between bone resorption and formation by secreting various cytokines that influence the functions of osteoclasts and osteoblasts. M1 macrophages secrete pro-inflammatory mediators such as Prostaglandin E2 (PGE2), TNF-α, IL-1β, IL-6, and IL-12, which favor osteoclastogenesis either directly or indirectly through modulation of the RANKL/OPG axis [23, 38]. In contrast, M2 macrophages suppress inflammatory responses by secreting cytokines such as IL-10, TGF-β, and vascular endothelial growth factor (VEGF), promote osteoblast differentiation and bone

ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

formation, and facilitate angiogenesis and tissue repair [23, 39, 40]. Therefore, the shift in the M1/M2 balance critically influences the direction of peri-implant bone metabolism.

3. Adaptive Immune Dysregulation in Peri-Implantitis

While the innate immune system initiates and propagates the inflammatory response, the subsequent involvement of adaptive immunity determines the chronicity and progression of tissue destruction in peri-implantitis. The adaptive immune system is distinguished by the establishment of immunological memory, a defining feature that enables lymphocytes to mount rapid and precise responses upon re-encounter with previously recognized antigens, thereby conferring long-term protection against reinfection [41]. The principal cellular components of adaptive immunity are lymphocytes, particularly T cells and B cells [42, 43]. Conventional αβ T cells are broadly categorized into $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells. $CD4^+$ T cells orchestrate diverse immune functions through the secretion of soluble mediators and direct cell–cell interactions, whereas $CD8^+$ T cells primarily eliminate infected or dysregulated cells through targeted cytotoxicity [41]. Upon exposure to pro-inflammatory signals, naïve $CD4^+$ T cells differentiate into distinct effector subsets—including Th1, Th2, and Th17—each mediating protective responses against bacterial, parasitic, and fungal infections. These differentiation pathways are governed by lineage-specific transcription factors (T-bet, GATA3, and RORγt) and are characterized by the production of signature cytokines and effector molecules [41, 44]. B cells contribute to adaptive immunity not only by secreting antibodies—soluble effector molecules that bind antigens with high affinity and promote pathogen neutralization and clearance—but also by functioning as antigen-presenting cells (APCs), internalizing specific antigens and presenting processed peptides to T cells, thereby bridging humoral and cellular immunity [42]. In peri-implantitis, adaptive immune activation occurs within a broader inflammatory milieu characterized by increased levels of proinflammatory cytokines (e.g., IL-1β, IL-6 and TNF-α), which are produced by activated lymphocytes together with myeloid and stromal cells [45]. These cytokines enhance osteoclastogenesis, promoting alveolar bone resorption and thereby contributing to disease progression [23].

3.1 Dendritic Cells: The Critical Bridge

Dendritic cells serve as essential antigen-presenting cells that link innate and adaptive immunity, playing a pivotal role in triggering T-cell responses [46]. Although they account for only a small fraction of the inflammatory infiltrate in peri-implantitis lesions, their presence indicates that adaptive immune mechanisms are actively engaged [47].

3.2 Imbalance in T lymphocyte subsets

T lymphocytes are the most abundant cell type in the inflammatory infiltrate characteristic of peri-implantitis lesions [47]. These cells encounter various exogenous stimuli—ranging from biofilm-derived antigens to titanium particles released from the implant surface—and respond by differentiating into specialized effector subsets. When their functional regulation goes awry, they become central drivers of tissue breakdown. Maintaining equilibrium between Th1 and Th2 cells is a fundamental aspect of immune regulation, a framework traditionally referred to as the Th1/Th2 paradigm. Under healthy conditions these two subsets exist in balance, yet this harmony is frequently disturbed in pathological states [48]. Th1 cells, distinguished by their expression of the transcription factor T-bet, secrete pro-inflammatory cytokines such as IFN-γ and TNF-α [49]. Through these mediators they activate macrophages and intensify inflammatory cascades, a profile typically observed during the early or stable phases of peri-implantitis [50, 51]. In contrast, Th2 cells produce a different set of cytokines—including interleukin-4 (IL-4), interleukin-5 (IL-5) and IL-13—which promote humoral immune responses and may contribute to chronic inflammatory remodeling in peri-implant lesions [6, 48]. Th2 cells are frequently linked to the chronic progression of peri-implant inflammatory lesions, where they participate both in reparative processes and in the perpetuation of chronic inflammation and fibrosis[6]. In a rat model of ligature-induced peri-implantitis, the submandibular lymph nodes were isolated and subsequently analyzed using real-time quantitative PCR along with flow cytometry. Their analysis revealed a significant increase in Th1 and Th17 cell numbers within the lymph nodes ($p < 0.05$), whereas Th2 cell counts declined over time. This shift likely reflects a more pronounced expansion of other Th subsets relative to the Th2 population [51].

As research into immune cell biology has advanced, the classical Th1/Th2 paradigm has been extended to include Th17/Treg cells [52]. Treg cells are essential for maintaining immune tolerance and

ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

limiting excessive inflammation. Their suppressive function is defined by the transcription factor FOXP3 and is mediated by immunosuppressive cytokines such as IL-10, TGF-β, and IL-35, allowing them to adapt to microenvironment-specific immune regulation [52, 53]. However, in peri-implantitis, Treg cells may exhibit a dissociation between their frequency and functional capacity. A recent study by Cafferata et al. demonstrated that, compared to healthy peri-implant tissues, peri-implantitis lesions showed upregulated expression of the Treg lineage-defining transcription factor FOXP3, yet downregulated expression of neuropilin-1—a co-stimulatory molecule associated with Treg function. Concurrently, levels of TGF-β1, a cytokine with potent immunosuppressive activity, were reduced [54]. This "high phenotype, low function" state was significantly associated with deeper probing depths and more severe bone defects, indicating that impaired Treg function compromises the suppression of destructive inflammation and directly contributes to disease progression [54]. Supporting this, Giro et al. also reported elevated FOXP3 expression in peri-implantitis tissues relative to healthy controls, suggesting recruitment or local expansion of Treg cells, albeit with insufficient functional capacity to control inflammation [55].

In contrast to functionally suppressed Treg cells, Th17 cells and their associated pro-inflammatory pathways are significantly activated in peri-implantitis. The characteristic transcription factor RORγt of Th17 is upregulated in peri-implantitis tissues [55]. Studies have demonstrated that the immune microenvironment of peri-implantitis exhibits a Th2/Th17-dominant pattern, with titanium ion levels in the PISF showing a positive correlation with Th17 activation. This suggests that foreign body stimulation may directly shape this pro-inflammatory T-cell response [56]. Mardegan et al. previously reported that the mRNA level of IL-23, a key inducer of Th17 differentiation in peri-implantitis tissues, was significantly higher than that in healthy controls [57]. Clinical intervention studies further confirmed that successful peri-implantitis treatment could significantly reduce the levels of Th17-associated effector cytokines (e.g., IL-17A, IL-1β and IL-6) in PISF [58]. Th17 cells strongly recruit neutrophils by secreting interleukin-17 (IL-17), synergistically promoting osteoclastogenesis and bone resorption, serving as a critical effector pathway driving peri-implant alveolar bone loss [6, 59, 60].

3.3 B Cells: Humoral Immunity and RANKL-Mediated Osteoclastogenesis

B cells account for approximately 10% of the inflammatory infiltrate in peri-implantitis lesions [47]. Their functional contributions to peri-implantitis include differentiation into plasma cells upon activation by local antigens, leading to the production of specific antibodies against pathogens within the peri-implant microbial biofilm [61]. B cells may also form immune complexes, indirectly exacerbating inflammatory responses by activating the complement system. More importantly, activated B cells themselves are significant participants in inflammation and bone destruction [62]. Studies have shown that $RANKL^+$ B lymphocytes accumulate in the peri-implant mucosa [63]. RANKL is a key factor in osteoclast differentiation and activation. Therefore, B cells directly contribute to peri-implant bone resorption by providing RANKL [63]. Furthermore, elevated levels of B cell activating factor (BAFF) in the saliva of patients with peri-implantitis further corroborate the active state of B cell-mediated immune responses in the disease [64].

4. Conclusion

This systematic review indicates that peri-implantitis is an inflammatory bone destruction disorder characterized by immune dysregulation. The immunopathological features are significantly different from periodontitis, showing stronger innate immune response and unique inflammatory microenvironment. Based on the above understanding, future therapeutic strategies are likely to increasingly shift from antimicrobial therapy and mechanical debridement toward host-modulating therapies. From a translational perspective, these immunological insights point toward promising therapeutic targets for precision immunotherapy in peri-implantitis. Strategies aimed at restoring the M1/M2 macrophage balance, enhancing Treg suppressive function, or blocking specific pro-inflammatory pathways—such as the CXCR2/CXCR1 neutrophil recruitment axis or Th17-associated cytokines—may offer novel approaches to disease management.

Future research should prioritize longitudinal studies that track immune dynamics throughout disease progression and in response to therapeutic intervention, as well as mechanistic investigations employing advanced models that recapitulate the unique peri-implant microenvironment. The integration of multi-omics approaches with spatial transcriptomics and single-cell resolution will further refine our understanding of cell–cell interactions and functional states within peri-implantitis

ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

lesions. Ultimately, a comprehensive understanding of the immunopathological mechanisms underlying peri-implantitis will inform the development of personalized immunomodulatory therapies capable of arresting disease progression, promoting tissue regeneration, and improving long-term implant outcomes.

Acknowledgement

This work was supported by Longgang District Science and Technology Plan (No. LGKCYLWS2024-31 and LGWJ2024-118).

References

[1] BERGLUNDH T, ARMITAGE G, ARAUJO M G, et al. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [J]. Journal of Clinical Periodontology, 2018, 45(S20).
[2] SALVI G E, STäHLI A, IMBER J C, et al. Physiopathology of peri-implant diseases [J]. Clin Implant Dent Relat Res, 2023, 25(4): 629-639.
[3] GALARRAGA-VINUEZA M E, PAGNI S, FINKELMAN M, et al. Prevalence, incidence, systemic, behavioral, and patient-related risk factors and indicators for peri-implant diseases: An AO/AAP systematic review and meta-analysis [J]. J Periodontol, 2025, 96(6): 587-633.
[4] CARCUAC O, BERGLUNDH T. Composition of Human Peri-implantitis and Periodontitis Lesions [J]. Journal of Dental Research, 2014, 93(11): 1083-1088.
[5] BERGLUNDH T, LINDHE J, ERICSSON I, et al. The soft tissue barrier at implants and teeth [J]. Clin Oral Implants Res, 1991, 2(2): 81-90.
[6] HUANG M, WANG C, LI P, et al. Role of immune dysregulation in peri-implantitis [J]. Front Immunol, 2024, 15: 1466417.
[7] CUNHA D M, SANTANA A P, GUERREIRO M M, et al. Reconceptualizing Peri-Implantitis: Dual-Factor Inflammation and Its Role in Advancing Biomaterial Coatings [J]. Clinical Implant Dentistry and Related Research, 2026, 28(1): e70108.
[8] MEHRNIA N, VAN DYKE T E. Microbial dysbiosis and immune dysregulation in periodontitis and peri-implantitis [J]. Front Cell Infect Microbiol, 2025, 15: 1678163.
[9] SU B, NG L G. Immunological modulation in health and disease [J]. Cellular & Molecular Immunology, 2023, 20(9): 981-982.
[10] ZHANG Q, CAO X. Epigenetic Remodeling in Innate Immunity and Inflammation [J]. Annual Review of Immunology, 2021, 39(1): 279-311.
[11] WU R, CHEN F, WANG N, et al. ACOD1 in immunometabolism and disease [J]. Cellular & Molecular Immunology, 2020, 17(8): 822-833.
[12] HERWALD H, EGESTEN A. Cells of Innate and Adaptive Immunity: A Matter of Class? [J]. Journal of Innate Immunity, 2017, 9(2): 109-110.
[13] CARPENTER S, O'NEILL L A J. From periphery to center stage: 50 years of advancements in innate immunity [J]. Cell, 2024, 187(9): 2030-2051.
[14] LI J, YE L J, DAI Y W, et al. Single-cell analysis reveals a unique microenvironment in peri-implantitis [J]. J Clin Periodontol, 2024, 51(12): 1665-1676.
[15] CHAPPLE I L C, HIRSCHFELD J, KANTARCI A, et al. The role of the host-Neutrophil biology [J]. Periodontol 2000, 2023, 00: 1-47.
[16] XIAO E, MATTOS M, VIEIRA G H A, et al. Diabetes Enhances IL-17 Expression and Alters the Oral Microbiome to Increase Its Pathogenicity [J]. Cell Host & Microbe, 2017, 22(1): 120-8.e4.
[17] HAJISHENGALLIS G. New developments in neutrophil biology and periodontitis [J]. Periodontology 2000, 2019, 82(1): 78-92.
[18] HEYMAN O, HOREV Y, MIZRAJI G, et al. Excessive inflammatory response to infection in experimental peri-implantitis: Resolution by Resolvin D2 [J]. Journal of Clinical Periodontology, 2022, 49(11): 1217-1228.
[19] LAWRENCE S M, CORRIDEN R, NIZET V. How Neutrophils Meet Their End [J]. Trends in Immunology, 2020, 41(6): 531-544.
[20] PARK S E, PARK K, KIM E, et al. CXCL5/CXCL8 induces neutrophilic inflammation in peri-implantitis [J]. J Periodontal Res, 2024, 59(4): 698-711.
[21] KIVELä-RAJAMäKI M, MAISI P, SRINIVAS R, et al. Levels and molecular forms of MMP-7 (matrilysin-1) and MMP-8 (collagenase-2) in diseased human peri-implant sulcular fluid [J]. J Periodontal Res, 2003, 38(6): 583-590.

ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

[22] HU X, SUN Y, XU W, et al. Expression of RANKL by peripheral neutrophils and its association with bone mineral density in COPD [J]. Respirology, 2016, 22(1): 126-132.
[23] LI Y, LI X, GUO D, et al. Immune dysregulation and macrophage polarization in peri-implantitis [J]. Front Bioeng Biotechnol, 2024, 12: 1291880.
[24] SUN X, GAO J, MENG X, et al. Polarized Macrophages in Periodontitis: Characteristics, Function, and Molecular Signaling [J]. Frontiers in Immunology, 2021, 12: 763334.
[25] YUNNA C, MENGRU H, LEI W, et al. Macrophage M1/M2 polarization [J]. European Journal of Pharmacology, 2020, 877: 173090.
[26] SICA A, MANTOVANI A. Macrophage plasticity and polarization: in vivo veritas [J]. Journal of Clinical Investigation, 2012, 122(3): 787-795.
[27] SHAPOURI-MOGHADDAM A, MOHAMMADIAN S, VAZINI H, et al. Macrophage plasticity, polarization, and function in health and disease [J]. Journal of Cellular Physiology, 2018, 233(9): 6425-6440.
[28] FRETWURST T, GARAICOA-PAZMINO C, NELSON K, et al. Characterization of macrophages infiltrating peri-implantitis lesions [J]. Clin Oral Implants Res, 2020, 31(3): 274-281.
[29] GALARRAGA-VINUEZA M E, OBREJA K, RAMANAUSKAITE A, et al. Macrophage polarization in peri-implantitis lesions [J]. Clin Oral Investig, 2021, 25(4): 2335-2344.
[30] DIONIGI C, LARSSON L, CARCUAC O, et al. Cellular expression of DNA damage/repair and reactive oxygen/nitrogen species in human periodontitis and peri-implantitis lesions [J]. J Clin Periodontol, 2020, 47(12): 1466-1475.
[31] YUAN S, WANG C, JIANG W, et al. Comparative Transcriptome Analysis of Gingival Immune-Mediated Inflammation in Peri-Implantitis and Periodontitis Within the Same Host Environment [J]. J Inflamm Res, 2022, 15: 3119-3133.
[32] CIESIELSKA A, MATYJEK M, KWIATKOWSKA K. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling [J]. Cellular and Molecular Life Sciences, 2020, 78(4): 1233-1261.
[33] PETTERSSON M, KELK P, BELIBASAKIS G N, et al. Titanium ions form particles that activate and execute interleukin-1β release from lipopolysaccharide-primed macrophages [J]. J Periodontal Res, 2017, 52(1): 21-32.
[34] EGER M, HIRAM-BAB S, LIRON T, et al. Mechanism and Prevention of Titanium Particle-Induced Inflammation and Osteolysis [J]. Front Immunol, 2018, 9: 2963.
[35] KHEDER W, BOUZID A, VENKATACHALAM T, et al. Titanium Particles Modulate Lymphocyte and Macrophage Polarization in Peri-Implant Gingival Tissues [J]. Int J Mol Sci, 2023, 24(14): 11644.
[36] RAMENZONI L L, FLüCKIGER L B, ATTIN T, et al. Effect of Titanium and Zirconium Oxide Microparticles on Pro-Inflammatory Response in Human Macrophages under Induced Sterile Inflammation: An In Vitro Study [J]. Materials (Basel), 2021, 14(15): 4166.
[37] CARRILLO-GáLVEZ A B, GUERRA-VALVERDE J A, PADIAL-MOLINA M, et al. Cross-talk between NLRP3 and AIM2 inflammasomes in macrophage activation by LPS and titanium ions [J]. Mol Med, 2025, 31(1): 223.
[38] OKA H, MIYAUCHI M, SAKAMOTO K, et al. PGE2 Activates Cementoclastogenesis by CementoblastsviaEP4 [J]. Journal of Dental Research, 2007, 86(10): 974-979.
[39] PARK M D, SILVIN A, GINHOUX F, et al. Macrophages in health and disease [J]. Cell, 2022, 185(23): 4259-4279.
[40] LI D, TAN X, ZHENG L, et al. A Dual-Antioxidative Coating on Transmucosal Component of Implant to Repair Connective Tissue Barrier for Treatment of Peri-Implantitis [J]. Adv Healthc Mater, 2023, 12(30): e2301733.
[41] CHI H, PEPPER M, THOMAS P G. Principles and therapeutic applications of adaptive immunity [J]. Cell, 2024, 187(9): 2052-2078.
[42] COOPER M D. The early history of B cells [J]. Nature Reviews Immunology, 2015, 15(3): 191-7.
[43] MILLER J F A P. The function of the thymus and its impact on modern medicine [J]. Science, 2020, 369(6503).
[44] DONG C. Cytokine Regulation and Function in T Cells [J]. Annual Review of Immunology, 2021, 39(1): 51-76.
[45] BERTOLDO B B, PAULO G O, FURTADO T C D S, et al. New immunological aspects of peri-implantitis [J]. einstein (São Paulo), 2024, 22: 1-7.
[46] YIN X, CHEN S, EISENBARTH S C. Dendritic Cell Regulation of T Helper Cells [J]. Annual Review of Immunology, 2021, 39(1): 759-790.
[47] GINESIN O, MAYER Y, GABAY E, et al. Revealing leukocyte populations in human peri-implantitis and periodontitis using flow cytometry [J]. Clin Oral Investig, 2023, 27(9): 5499-5508.
[48] RUTERBUSCH M, PRUNER K B, SHEHATA L, et al. In Vivo CD4+T Cell Differentiation and

ISSN 2618-1584 Vol. 8, Issue 2: 92-99, DOI: 10.25236/FMSR.2026.080211

Function: Revisiting the Th1/Th2 Paradigm [J]. Annual Review of Immunology, 2020, 38(1): 705-25.
[49] BUTCHER M J, ZHU J. Recent advances in understanding the Th1/Th2 effector choice [J]. Faculty Reviews, 2021, 10: 30.
[50] WANG C W, HAO Y, DI GIANFILIPPO R, et al. Machine learning-assisted immune profiling stratifies peri-implantitis patients with unique microbial colonization and clinical outcomes [J]. Theranostics, 2021, 11(14): 6703-6716.
[51] ZHANG H, SUN M, XU H, et al. Th-Cell Subsets of Submandibular Lymph Nodes in Peri-Implantitis [J]. Journal of Craniofacial Surgery, 2024, 35(2): 692-698.
[52] DIKIY S, RUDENSKY A Y. Principles of regulatory T cell function [J]. Immunity, 2023, 56(2): 240-255.
[53] MAI J. Th 17 cells interplay with Foxp3+ Tregs in regulation of inflammation and autoimmunity [J]. Frontiers in Bioscience, 2010, 15(1): 986-1006.
[54] CAFFERATA E A, RAMANAUSKAITE A, PARVINI P, et al. Impaired Treg-Mediated Immune Regulation in Peri-Implantitis Lesions and Implant Loss: Insights From Histological and Molecular Analyses [J]. J Clin Periodontol, 2025, 52(12): 1779-1790.
[55] GIRO G, TEBAR A, FRANCO L, et al. Treg and TH17 link to immune response in individuals with peri-implantitis: a preliminary report [J]. Clin Oral Investig, 2021, 25(3): 1291-1297.
[56] CASARIN R C V, BONILHA G M, PAZ H, et al. Unraveling the Microbial Mosaic and Inflammatory Core of Peri-implantitis [J]. J Dent Res, 2026, 105(2): 267-275.
[57] MARDEGAN G P, SHIBLI J A, ROTH L A, et al. Transforming growth factor-β, interleukin-17, and IL-23 gene expression profiles associated with human peri-implantitis [J]. Clin Oral Implants Res, 2017, 28(7): e10-e5.
[58] GONçALVES L, NEVES G S T, DA SILVA A M P, et al. The Effect of Peri-Implant Therapy on the Expression of Th17-Related Cytokines in Patients with Peri-Implant Mucositis and Peri-Implantitis: A Prospective Longitudinal Study [J]. J Clin Med, 2025, 14(2): 340.
[59] YU T, ACHARYA A, MATTHEOS N, et al. Molecular mechanisms linking peri-implantitis and type 2 diabetes mellitus revealed by transcriptomic analysis [J]. PeerJ, 2019, 7: e7124.
[60] DJINIC KRASAVCEVIC A, NIKOLIC N, MILINKOVIC I, et al. Notch signalling cascade and proinflammatory mediators in peri-implant lesions with different RANKL/OPG ratios-An observational study [J]. J Periodontal Res, 2023, 58(2): 360-368.
[61] CHEN G, ZHAO X, YANG B, et al. Peri-implant diseases triggered by oral microdysbiosis: pathogenesis and precision intervention strategies [J]. Front Microbiol, 2025, 16: 1639095.
[62] CHEN D, WU X, LIU Q, et al. Memory B Cell as an Indicator of Peri-implantitis Status: A Pilot Study [J]. Int J Oral Maxillofac Implants, 2021, 36(1): 86-93.
[63] HEYMAN O, HOREV Y, KOREN N, et al. Niche Specific Microbiota-Dependent and Independent Bone Loss around Dental Implants and Teeth [J]. J Dent Res, 2020, 99(9): 1092-1101.
[64] TITUSSON C, JANSSON L, MODIN C, et al. Salivary Inflammatory Mediator Profiles in Periodontal and Peri-Implant Health and Disease: A Cross-Sectional Study [J]. Clin Implant Dent Relat Res, 2025, 27(1): e70002.