DYSBIOSIS-DRIVEN IMMUNE REPROGRAMMING AND OSTEOIMMUNE TISSUE DESTRUCTION IN PERIODONTITIS: SINGLE-CELL INSIGHTS AND PROSPECTS FOR PRECISION HOST MODULATION

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Abstract

Background

Periodontitis is a chronic dysbiosis-associated immunoinflammatory disease characterized by the progressive destruction of gingival connective tissue, periodontal ligament, cementum, and alveolar bone. Contemporary evidence indicates that periodontal tissue damage cannot be explained solely by the direct pathogenic activity of individual bacterial species. Instead, disease development is determined by reciprocal interactions between a dysbiotic subgingival microbial community, impaired epithelial barrier function, dysregulated innate and adaptive immunity, metabolic reprogramming of immune and stromal cells, and failure of inflammation resolution.

The current concept of periodontal pathogenesis therefore shifts from a pathogen-centred model toward a network model of microbial–immune–stromal interactions. In this model, inflammation changes the local nutritional and metabolic environment, thereby supporting the persistence of inflammophilic microorganisms. The dysbiotic microbiota, in turn, continuously stimulates immune pathways and maintains a self-amplifying cycle of inflammation and tissue destruction.

Objective

To summarize contemporary evidence on dysbiosis-driven immune reprogramming in periodontitis, focusing on structural immunity, neutrophil extracellular traps, macrophage immunometabolism, inflammasome activation, T-cell plasticity, trained immunity, and RANKL-mediated osteoclastogenesis, as well as to identify potential targets for precision host-modulating therapy.

Materials and Methods

A structured integrative search of PubMed/MEDLINE, Scopus, Web of Science Core Collection, and Embase was designed using combinations of the following terms: “periodontitis,” “oral dysbiosis,” “immune reprogramming,” “single-cell RNA sequencing,” “spatial transcriptomics,” “neutrophil extracellular traps,” “macrophage polarization,” “immunometabolism,” “NLRP3 inflammasome,” “Th17 cells,” “trained immunity,” “RANKL,” and “osteoimmunology.”

Publications from 2020 to 2026 were prioritized, while landmark earlier studies were included to clarify the evolution of major pathogenetic concepts. Human clinical and transcriptomic studies, experimental animal investigations, in vitro mechanistic studies, and high-quality systematic and integrative reviews were considered. Findings were synthesized according to major microbial, cellular, molecular, and osteoimmune pathways.

Results and Discussion

The analyzed evidence supports the concept that periodontitis begins with disruption of the normally balanced relationship between the subgingival microbiota and periodontal immunity. Keystone pathogens, accessory microorganisms, and inflammophilic pathobionts alter complement activity, Toll-like receptor signaling, epithelial integrity, and leukocyte function. This disturbance promotes microbial persistence without necessarily causing complete immune suppression.

Gingival epithelial cells and fibroblasts are now recognized as active components of periodontal immunity rather than passive structural elements. Keratinocytes express pattern-recognition receptors, produce antimicrobial peptides, and regulate the recruitment of neutrophils and lymphocytes through cytokines and chemokines. Recent single-cell and spatial transcriptomic studies have identified distinct disease-associated populations of junctional and sulcular keratinocytes and have demonstrated spatially organized immune microniches around the tooth–gingiva interface.

Periodontal fibroblasts also exhibit considerable functional heterogeneity. Proinflammatory fibroblast populations enriched in CXCL8, CXCL10, CXCL13, and related chemokine pathways may recruit neutrophils, T cells, B cells, and plasma cells into periodontal lesions. Consequently, fibroblasts participate directly in the formation and maintenance of chronic inflammatory niches rather than acting exclusively as extracellular matrix-producing cells.

Neutrophils represent the dominant innate immune population at the gingival barrier. Controlled neutrophil recruitment is required for microbial containment. However, persistent activation promotes the release of reactive oxygen species, matrix-degrading proteases, myeloperoxidase, and neutrophil extracellular traps. NETs contain extracellular DNA, antimicrobial proteins, and histones. Experimental evidence indicates that extracellular histones derived from NETs can stimulate pathogenic IL-17-dominated inflammation and accelerate periodontal bone destruction.

Macrophages demonstrate substantial phenotypic and metabolic plasticity. Proinflammatory macrophage states are associated with enhanced glycolysis, oxidative stress, and production of IL-1β, IL-6, TNF-α, and chemokines. Reparative macrophage populations support efferocytosis, angiogenesis, extracellular matrix remodeling, and tissue regeneration. Therefore, the traditional M1/M2 classification is insufficient to describe the full spectrum of macrophage states within periodontal lesions.

Activation of the NLRP3 inflammasome represents another central mechanism. Microbial products provide inflammasome-priming signals through Toll-like receptors and NF-κB, whereas mitochondrial dysfunction, extracellular ATP, potassium efflux, oxidative stress, and lysosomal injury provide activation signals. NLRP3 activation leads to caspase-1-dependent maturation of IL-1β and IL-18 and may induce pyroptotic cell death. These events amplify leukocyte recruitment, stromal-cell dysfunction, and osteoclastogenic signaling.

The Th17–IL-17 pathway has a dual and context-dependent role. Physiological IL-17 signaling supports epithelial defence and neutrophil recruitment. Persistent or excessive Th17 activity, however, increases the production of IL-1β, TNF-α, chemokines, matrix metalloproteinases, and receptor activator of nuclear factor-κB ligand. An imbalance between Th17 cells and regulatory T cells may therefore sustain chronic inflammation.

Recent experimental evidence has further demonstrated that Th17 cells possess location-dependent functional plasticity. A subset of Th17-lineage cells may differentiate into T follicular helper-like cells within draining lymph nodes. These cells support protective antibody production and help restrict the total oral microbial biomass. Thus, complete pharmacological suppression of the Th17 pathway could eliminate both pathogenic and protective immune functions.

Periodontal bone destruction occurs at the interface between immunity and bone metabolism. Activated T cells, B cells, fibroblasts, periodontal ligament cells, and osteoblast-lineage cells produce RANKL. Binding of RANKL to RANK on osteoclast precursors activates NF-κB and NFATc1 signaling and promotes osteoclast differentiation. Simultaneous reduction of osteoprotegerin activity shifts the RANKL/OPG balance toward pathological bone resorption.

Single-cell studies demonstrate that osteoclast precursors, macrophages, endothelial cells, fibroblasts, mesenchymal stromal cells, and lymphocyte subsets form highly organized cellular communication networks. The severity of bone loss may therefore depend not only on cytokine concentration but also on the spatial localization and functional state of specific cell populations.

Trained immunity is an additional emerging mechanism. Repeated exposure to periodontal microorganisms and inflammatory mediators may cause long-term epigenetic and metabolic reprogramming of monocytes, macrophages, bone-marrow progenitors, and gingival stromal cells. Such inflammatory memory may explain exaggerated responses to repeated microbial stimulation, recurrence of inflammation, and possible links between periodontitis and systemic inflammatory diseases.

These findings support the development of precision host-modulating therapies. Potential strategies include local regulation of complement signaling, selective inhibition of excessive NLRP3 activity, neutralization of extracellular NET-associated histones, reprogramming of macrophage metabolism, restoration of Th17/Treg balance, correction of the RANKL/OPG ratio, and application of specialized pro-resolving lipid mediators. Biomaterial-based local delivery systems may improve therapeutic selectivity while minimizing systemic immunosuppression.

Conclusion

Periodontitis is a spatially organized, dysbiosis-driven immunoinflammatory disease involving persistent reprogramming of epithelial, stromal, innate immune, adaptive immune, and bone-resorbing cell populations. Its progression is associated with excessive neutrophil activation, NET formation, macrophage immunometabolic dysfunction, NLRP3 inflammasome signaling, maladaptive Th17 responses, and RANKL-dependent osteoclastogenesis.

Single-cell and spatial-omics technologies have revealed previously unrecognized periodontal cell populations and inflammatory microniches. These findings create a scientific basis for moving from generalized anti-inflammatory therapy toward personalized and locally delivered host modulation. Future interventions should suppress destructive immune pathways while preserving antimicrobial defence, immune resolution, and periodontal tissue regeneration.

Keywords: periodontitis, oral dysbiosis, immune reprogramming, single-cell transcriptomics, structural immunity, neutrophil extracellular traps, macrophage immunometabolism, NLRP3 inflammasome, Th17 plasticity, trained immunity, RANKL, osteoimmunology.

References

1. Easter QT, Fernandes Matuck B, Stark GB, et al. Single-cell and spatially resolved interactomics of tooth-associated keratinocytes in periodontitis. Nature Communications. 2024;15:5016. doi:10.1038/s41467-024-49037-y.
2. Kim TS, Silva LM, Theofilou VI, et al. Neutrophil extracellular traps and extracellular histones potentiate IL-17 inflammation in periodontitis. Journal of Experimental Medicine. 2023;220(9). doi:10.1084/jem.20221751.
3. McClure FA, et al. Th17-to-Tfh plasticity during periodontitis limits disease through enhanced protective antibody responses. Journal of Experimental Medicine. 2024;221(8). doi:10.1084/jem.20232015.
4. Caetano AJ, et al. Spatially resolved transcriptomics reveals pro-inflammatory fibroblast involvement in lymphocyte recruitment through CXCL8 and CXCL10. eLife. 2023;12. doi:10.7554/eLife.81525.
5. Chen Y, Wang H, Yang Q, et al. Single-cell RNA landscape of the osteoimmunology microenvironment in periodontitis. Theranostics. 2022;12(3):1074–1096. doi:10.7150/thno.65694.
6. Li Y, et al. Roles of trained immunity in the pathogenesis of periodontitis. Journal of Periodontal Research. 2023;58(5):864–876. doi:10.1111/jre.13158.
7. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nature Reviews Immunology. 2021;21:426–440.