ISSN 0973-2063 (online) 0973-8894 (print)

Bioinformation 22(11): 8770-8774 (2026)

©Biomedical Informatics (2026)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

BIOMEDICAL INFORMATICS

www.bioinformation.net

Volume 22(11)

Review

Received November 01, 2026; Revised November 30, 2026; Accepted November 30, 2026, Published November 30, 2026

DOI: 10.6026/973206300228770

SJIF 2026 (Scientific Journal Impact Factor for 2026) is 8.677
ABCD 2026 index is 7.183
EA 2025 score is 0.37
2025 EA ranking:
72 of 353 in General Dentistry (associated subject; top 20.4%)
2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

Declaration on Publication Ethics:
The author's state that they adhere with COPE guidelines on publishing ethics as described elsewhere at https://publicationethics.org/. The authors also undertake that they are not associated with any other third party (governmental or non-governmental agencies) linking with any form of unethical issues connecting to this publication. The authors also declare that they are not withholding any information that is misleading to the publisher in regard to this article.

Declaration on official E-mail:
The corresponding author declares that lifetime official e-mail from their institution is not available for all authors

License statement:
This is an Open Access article which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. This is distributed under the terms of the Creative Commons Attribution License

Comments from readers:
Articles published in BIOINFORMATION are open for relevant post publication comments and criticisms, which will be published immediately linking to the original article without open access charges. Comments should be concise, coherent and critical in less than 1000 words.

Disclaimer:
Bioinformation provides a platform for scholarly communication of data and information to create knowledge in the Biological/Biomedical domain after adequate peer/editorial reviews and editing entertaining revisions where required. The views and opinions expressed are those of the author(s) and do not reflect the views or opinions of Bioinformation and (or) its publisher Biomedical Informatics. Biomedical Informatics remains neutral and allows authors to specify their address and affiliation details including territory where required.

Edited by Ruby Singh
E-mail: bioinformationruby@gmail.com
Citation: Dayakar *et al*. Bioinformation 22(11): 8770-8774(2026)

Single-cell and spatial multi-omics: Redefining precision periodontology: A review

Mundoor Manjunath Dayakar*, Prakash Pai Gurupur, K. Vinesh Kamath, Radhika M. Priyadarshini Sooranagi, V. Sanjana & Pallavi Holal

[1]Department of Periodontology, K.V.G. Dental College and Hospital, Sullia, Rajiv Gandhi University of Health Sciences, Karnataka, India; *Corresponding author

Affiliation URL:
https://kvgdentalcollege.org/

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 22(11): 8770-8774 (2026)
©Biomedical Informatics (2026)

Author contact:
Mundoor Manjunath Dayakar - E-mail: mmdayakar@yahoo.com
Prakash Pai Gurupur - E-mail: prakashpaipai2014@gmail.com
K. Vinesh Kamath - E-mail: drkamath84@gmail.com
Radhika Priyadarshini M. Sooranagi - E-mail: radhika156priya@gmail.com
V. Sanjana - E-mail: sanjanav8197@gmail.com
Pallavi Holal - E-mail: pallaviholal9@gmail.com

Abstract:
Periodontitis is a chronic inflammatory disease whose molecular heterogeneity is poorly captured by conventional clinical assessment. Single-cell and spatial multi-omics enable high-resolution analysis of periodontal tissues at cellular and positional levels. These technologies reveal pathogenic fibroblasts, stromal–neutrophil interactions, altered keratinocytes and osteoimmune niches. They support biomarker discovery, patient stratification, host-modulation therapy and improved understanding of peri-implant disease. Thus, standardized methods, diverse cohorts and prospective validation are needed to establish their role in precision periodontology.

Keywords: Periodontitis, single-cell RNA sequencing, spatial transcriptomics, spatial proteomics, multi-omics, precision periodontology, host–microbe interaction, gingival

Background:
Periodontitis is one of the most prevalent chronic inflammatory diseases of humans and a major cause of tooth loss in adults **[1]**. It arises when a dysbiotic subgingival biofilm triggers a dysregulated host response that destroys the connective tissue attachment and alveolar bone and it is increasingly recognised as a local disease with systemic consequences, being linked to diabetes, cardiovascular disease and other inflammatory comorbidities **[2]**. Although the current classification system has introduced staging and grading to describe severity, complexity and rate of progression, patients with similar clinical parameters frequently differ in susceptibility, speed of destruction and response to therapy **[3]**. This clinical heterogeneity reflects biological heterogeneity at the tissue level that conventional diagnostic tools cannot resolve. For over two decades, the molecular biology of periodontitis was studied mainly through histology, immunohistochemistry, gingival crevicular fluid analysis and bulk transcriptomics of gingival biopsies **[4]**. Bulk approaches measure the average expression of all cells in a sample, so a change in gene expression may reflect a true change in cell behaviour, a shift in cell proportions, or both **[5]**. Rare but biologically decisive populations are diluted and the spatial relationships between epithelium, stroma, vasculature, immune cells and bacteria are lost during tissue homogenisation **[6]**. The emergence of single-cell and spatial technologies, together with coordinated initiatives such as the Human Oral and Craniofacial Cell Atlas, has begun to overcome these limitations and provide cell-resolved reference maps of oral tissues **[7]**. Therefore, it is of interest to examine the single-cell and spatial multi-omics technologies, their contributions to understanding periodontal health and disease and their potential to support precision periodontology.

The periodontium as a multicellular ecosystem:
The periodontium is a structurally complex organ composed of the gingival epithelium (oral, sulcular and junctional), the gingival lamina propria, the periodontal ligament, cementum and alveolar bone **[8]**. Each compartment contains multiple resident cell types, including keratinocytes, fibroblasts, endothelial cells, pericytes, nerves, osteoblasts and osteoclasts, together with tissue-resident and recruited immune cells **[9]**. The junctional epithelium is unique in being attached to the tooth surface and in continuous contact with the subgingival biofilm, while the underlying connective tissue receives constant microbial and mechanical stimulation **[10, 11]**. Health therefore represents a dynamic equilibrium rather than an absence of inflammation and disease reflects a failure of multicellular regulation rather than the behaviour of a single cell type **[12]**. Understanding which cells change, where they are located and how they communicate is central to explaining why some sites and individuals progress while others remain stable.

Principles of single-cell technologies:
Single-cell RNA sequencing (scRNA-seq) captures the transcriptome of individual cells after enzymatic and mechanical dissociation of tissue. In widely used droplet-based systems, single cells are encapsulated with barcoded beads so that each transcript is tagged with a cell barcode and a unique molecular identifier, enabling thousands of cells to be profiled in parallel **[13]**. After quality control, normalisation, dimensionality reduction and clustering, cells are annotated using canonical marker genes and reference atlases. Downstream analyses include differential expression between health and disease, trajectory or pseudotime inference to model differentiation or activation states, gene regulatory network inference and ligand–receptor analysis to predict cell–cell communication **[14, 15]**. Single-cell multi-omics extends this approach by measuring more than one molecular layer in the same cell. Cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) links transcriptomes to surface protein expression, single-cell assays for transposase-accessible chromatin (scATAC-seq) and combined multiome assays connect gene expression to chromatin accessibility and paired T-cell and B-cell receptor sequencing tracks clonal expansion of lymphocytes **[16, 17]**. For

periodontology, these modalities are valuable because immune activation, epigenetic memory of inflammation and antigen-driven lymphocyte responses are all thought to influence disease persistence. Best-practice frameworks for data processing, integration of multiple samples and correction of batch effects are now available and are important for producing reproducible periodontal atlases.

Spatial transcriptomics and spatial proteomics:

The principal limitation of scRNA-seq is that dissociation removes cells from their anatomical context. Spatial transcriptomics addresses this by measuring gene expression directly in tissue sections. Sequencing-based methods capture messenger RNA on arrays of spatially barcoded spots or nanoballs and can measure the whole transcriptome, although each capture unit may contain several cells depending on platform resolution **[18]**. Imaging-based methods use multiplexed in situ hybridisation to detect targeted gene panels at single-cell or subcellular resolution **[19]**. The historical development and relative strengths of these platforms have been comprehensively catalogued. Spatial proteomics complements these methods by imaging tens of proteins in a single section using cyclic immunofluorescence or metal-tagged antibodies with imaging mass cytometry **[20]**. Computational integration of single-cell and spatial data, through deconvolution of spots or mapping of annotated single-cell references onto tissue, allows cell identities defined by scRNA-seq to be placed back into their native niches **[21-24]**. The combination of dissociated single-cell profiling with spatial read-outs is now referred to as spatial multi-omics and forms the technical basis for most recent periodontal atlases **(Table 1).**

Table 1: Single-cell and spatial multi-omics technologies applied to periodontal research

Technology class	Representative platforms	Read-out and resolution	Principal use in periodontal research
Single-cell transcriptomics	Droplet-based scRNA-seq, plate-based full-length scRNA-seq, single-nucleus RNA-seq	Whole-transcriptome profile of individual dissociated cells or nuclei	Cell atlases of gingival, oral mucosa and periodontal ligament; discovery of disease-associated subsets
Single-cell multi-omics	CITE-seq (RNA + surface protein), scATAC-seq and multiome (RNA + chromatin), TCR/BCR repertoire sequencing	Two or more molecular layers from the same cell	Linking gene regulation, surface phenotype and clonality of immune and stromal cells
Sequencing-based spatial transcriptomics	Spot arrays (e.g., Visium), high-density nanoball arrays (e.g., Stereo-seq), bead arrays	Transcriptome-wide capture on tissue sections; multicellular spots to near-cellular bins	Mapping epithelial, stromal and immune compartments of healthy and diseased gingival

Single-cell atlases of the human gingival **and oral mucosa:**

A landmark study generated a single-cell atlas of human oral mucosal tissues, including gingival from healthy individuals and patients with periodontitis **[25]**. It demonstrated that oral barrier tissues have site-specific cellular programmes and identified a stromal–neutrophil axis, in which activated stromal cells in inflamed gingival participate in orchestrating neutrophil recruitment. This finding repositioned fibroblasts and other structural cells from passive scaffolding to active regulators of periodontal immunity **[26, 27]**. In parallel, single-cell profiling of healthy and inflamed oral tissues defined the heterogeneity of mesenchymal and epithelial populations and showed how these populations remodel in response to chronic inflammatory disease **[28]**. Further studies expanded these observations across populations and disease states. Single-cell analysis of gingival tissue from Asian patients with chronic periodontitis identified inflammation-promoting subsets among immune and stromal cells **[29]**, emphasising the value of profiling diverse cohorts. A study profiling 51,248 cells from healthy controls, patients with severe periodontitis and patients shortly after initial periodontal therapy mapped the osteoimmunology microenvironment and documented changes in mesenchymal, immune and bone-related populations with treatment. These atlases together provide the first reference maps against which individual patient samples may eventually be compared.

Stromal cells as orchestrators of periodontal inflammation:

One of the most consistent messages from single-cell periodontology is the central role of fibroblasts. Beyond the stromal–neutrophil axis described in human gingival **[30]**, a mouse gingival single-cell atlas identified an activated fibroblast subpopulation that guides oral barrier immunity in experimental periodontitis **[31]**. Spatial studies reinforced this concept by combining scRNA-seq, spot-based spatial transcriptomics and high-resolution multiplex fluorescence in situ hybridisation. This work defined specialised epithelial and stromal compartments within the lamina propria and spatially mapped a rare pathogenic fibroblast population located in a highly immunogenic region, which expressed CXCL8 and CXCL10 and was implicated in lymphocyte recruitment and pathological angiogenesis **[32]**. Such inflammatory fibroblasts represent attractive targets because they may sustain inflammation after the initial microbial trigger has been reduced **[33]**.

The epithelial barrier: sulcular and junctional keratinocytes:

The tooth-associated epithelium was historically underrepresented in single-cell datasets because of its small size and difficulty of sampling. An integrated atlas of the human periodontium comprising 34 samples and 105,918 cells specifically resolved sulcular and junctional keratinocytes and showed that, in periodontitis, these cells display altered differentiation states and are enriched for effector cytokines. Ligand–receptor analysis predicted keratinocyte-specific interactions with innate and adaptive immune cells, suggesting that the epithelium acts as an immune signalling hub rather than a simple physical barrier **[34]**. Complementary work integrating scRNA-seq, spatial transcriptomics and spatial proteomics across human and mouse gingival identified an epithelial JAG1–Notch pathway that modulates macrophage behaviour; local inhibition of JAG1 reduced periodontal inflammation and alveolar bone

loss in a ligature model **[35]**. These findings illustrate how single-cell and spatial data can progress from description to mechanistically testable therapeutic targets.

The immune compartment at single-cell resolution:
Periodontitis lesions contain a dense and heterogeneous infiltrate of neutrophils, macrophages, T cells, B cells and plasma cells. Single-cell atlases have resolved B-cell and plasma-cell heterogeneity in periodontitis, supporting the long-standing histological observation that plasma cells dominate established lesions and providing molecular definitions for their subsets **[25, 9]**. Macrophage states have also been profiled in patients with periodontitis and type 2 diabetes, providing cellular insight into the bidirectional relationship between the two diseases **[36]**. Single-cell atlases of the osteoimmune microenvironment further connect immune activation with changes in mesenchymal and bone-related cells **[9]**. Because neutrophils are fragile and poorly captured by some dissociation protocols, their contribution is probably underestimated in current datasets, an important caveat when interpreting immune proportions **[13, 32]**.

Spatial architecture of the diseased periodontium:
Spatial technologies have added positional information that cannot be inferred from dissociated cells. A Stereo-seq atlas of human gingival from healthy individuals and patients with periodontitis resolved the major epithelial, stromal, endothelial and immune compartments in situ and showed that inflammation-related JAK-STAT and NF-κB signalling pathways were upregulated in endothelial cells in periodontitis **[37]**, highlighting the vasculature as an active participant in disease. Highly multiplexed immunofluorescence with 33 antibodies revealed peri-epithelial immune foci, innate immune cells spatially constrained around junctional keratinocytes, immunosuppressed junctional keratinocyte micro-niches and tertiary lymphoid structures localised near the sulcular epithelium in periodontitis **[8, 20]**. Spatial mapping also localised inflammatory fibroblasts to discrete immunogenic regions of the lamina propria **[32]**. Together, these studies indicate that periodontitis is organised into structured inflammatory neighbourhoods rather than a diffuse infiltrate.

Host–microbe interactions at single-cell resolution:
Periodontitis is initiated by dysbiosis, yet most microbiome studies analyse bacteria separately from host tissue. Single-cell metagenomics applied to periodontal tissues detected 37 bacterial species with cell-specific tropism and fluorescence in situ hybridisation identified intracellular bacterial 16S rRNA signals that correlated with pro-inflammatory keratinocyte phenotypes *in situ* **[8]**. This approach directly links the presence of particular microbes within specific host cells to local inflammatory states, providing a new level of resolution for studying pathobionts and keystone pathogens and for understanding how the same microbial community can produce different host responses at different sites **[38, 12]**.

Systemic and environmental modifiers:
Precision periodontology must account for risk factors that modify disease expression. Single-cell profiling of macrophages in patients with periodontitis and type 2 diabetes offers a cellular explanation for the aggravating effect of hyperglycaemia on periodontal inflammation **[36]**. A single-cell spatial atlas of gingival tissue from smokers described smoking-associated alterations in the cellular composition and spatial organisation of the gingival, providing insight into why smokers show greater attachment loss yet frequently exhibit reduced clinical signs of inflammation **[39]**. Such data may eventually allow risk factors to be represented as measurable tissue signatures rather than as categorical modifiers in grading.

Peri-implant disease:
Peri-implantitis progresses faster than periodontitis and responds less predictably to treatment, yet its biology has been studied far less. Single-cell analysis of peri-implantitis tissue has revealed a distinct cellular microenvironment compared with periodontitis **[40]**, supporting the view that peri-implant disease is not simply periodontitis around an implant. Cell-resolved comparison of the two conditions may help explain differences in progression and guide implant-specific host-modulation strategies.

Cross-species translation and animal models:
Ligature-induced periodontitis in mice remains the most widely used model for mechanistic experiments, but its relevance to human disease has been debated. Single-cell and spatial studies now permit direct comparison of cell types and transcriptional programmes between species. The mouse gingival atlas identified fibroblast behaviours that parallel observations in human tissue **[41]**, whereas integrated human and mouse multi-omics revealed both conserved and divergent features of periodontal inflammation, emphasising that targets identified in mice should be verified against human atlases before clinical development **[42]**.

Translational implications for precision periodontology:
Biomarker discovery:
Cell-type-specific genes identified in single-cell and spatial atlases, such as chemokines produced by inflammatory fibroblasts or effector cytokines expressed by tooth-associated keratinocytes, may serve as candidate biomarkers **[32, 8]**. Because many of these molecules are secreted, they could be translated into gingival crevicular fluid or salivary assays that report the activity of specific pathogenic cell states rather than non-specific inflammation.

Challenges and limitations:
Despite rapid progress, several obstacles restrict clinical translation. Enzymatic dissociation can alter gene expression and preferentially lose fragile cells such as neutrophils, while small gingival biopsies yield limited cell numbers. Sequencing-based spatial platforms may capture several cells per spot, requiring computational deconvolution, whereas imaging-based platforms

measure predefined gene panels. Most periodontal studies include relatively few patients, sample different anatomical sites and use varied clinical definitions, making cross-study comparison difficult. Batch effects, inconsistent cell annotation and the absence of harmonised reference atlases add further variability. Almost all current datasets are cross-sectional, so causal relationships and temporal sequences of disease progression remain uncertain. Cost, turnaround time and the need for specialised bioinformatic expertise limit accessibility, particularly in low-resource settings. Finally, the generation of genomic data from patient tissue raises ethical considerations relating to consent, privacy and data sharing, which must be addressed as datasets become larger and more integrated.

Conclusion:

Single-cell and spatial multi-omics have transformed the understanding of periodontitis from a disease described by clinical measurements into a spatially organised network of interacting epithelial, stromal, vascular, immune and microbial components. These technologies have identified inflammatory fibroblasts, altered tooth-associated keratinocytes, immune niches and tertiary lymphoid structures and have already produced candidate therapeutic targets. Although standardisation, larger longitudinal cohorts and clinical validation are still required, single-cell and spatial multi-omics provide a strong biological foundation for precision periodontology and are likely to shape futsure diagnosis, patient stratification and targeted host-modulation therapy.

References:

[1] Nazir M *et al. ScientificWorldJournal.* 2020 **2020**:2146160. [PMID: 32549797]
[2] Hajishengallis G & Chavakis T. *Nat Rev Immunol.* 2021 **21**:426. [PMID: 33510490]
[3] Loos BG & Van Dyke TE. *Periodontol 2000.* 2020 **83**:26. [PMID: 32385877]
[4] Caetano AJ *et al. J Periodontal Res.* 2022 **57**:1210. [PMID: 36170299]
[5] Vandereyken K *et al. Nat Rev Genet.* 2023 **24**:494. [PMID: 36864178]
[6] Rao A *et al. Nature.* 2021 **596**:211. [PMID: 34381231]
[7] Huang N *et al. Nat Med.* 2021 **27**:892. [PMID: 33767405]
[8] Easter QT *et al. Nat Commun.* 2024 **15**:5016. [PMID: 38876998]
[9] Chen Y *et al. Theranostics.* 2022 **12**:1074. [PMID: 35154475]
[10] Yuan X *et al. J Dent Res.* 2021 **100**:209. [PMID: 32985318]
[11] Tanaka K *et al. Sci Rep.* 2021 **11**:18860. [PMID: 34552180]
[12] Curtis MA *et al. Periodontol 2000.* 2020 **83**:14. [PMID: 32385883]
[13] Greenwell-Wild T *et al. STAR Protoc.* 2021 **2**:100908. [PMID: 34746866]
[14] Heumos L *et al. Nat Rev Genet.* 2023 **24**:550. [PMID: 37002403]
[15] Browaeys R *et al. Nat Methods.* 2020 **17**:159. [PMID: 31819264]
[16] Hao Y *et al. Cell.* 2021 **184**:3573. [PMID: 34062119]
[17] Thompson SM *et al. J Invest Dermatol.* 2022 **142**:1812. [PMID: 34922949]
[18] Chen a *et al. Cell.* 2022 **185**:1777. [PMID: 35512705]
[19] Janesick A *et al. Nat Commun.* 2023 **14**:8353. [PMID: 38114474]
[20] Black S *et al. Nat Protoc.* 2021 **16**:3802. [PMID: 34215862]
[21] Zhao E *et al. Nat Biotechnol.* 2021 **39**:1375. [PMID: 34083791]
[22] Kleshchevnikov V *et al. Nat Biotechnol.* 2022 **40**:661. [PMID: 35027729]
[23] Dries R *et al. Genome Biol.* 2021 **22**:78. [PMID: 33685491]
[24] Fawkner-Corbett D *et al. Cell.* 2021 **184**:810. [PMID: 33406409]
[25] Williams DW *et al. Cell.* 2021 **184**:4090. [PMID: 34129837]
[26] Krausgruber T *et al. Nature.* 2020 **583**:296. [PMID: 32612232]
[27] Davidson S *et al. Nat Rev Immunol.* 2021 **21**:704. [PMID: 33911232]
[28] Caetano AJ *et al. Elfie.* 2021 **10**:e62810. [PMID: 33393902]
[29] Qian SJ *et al. Front Immunol.* 2021 **12**:711337. [PMID: 34566966]
[30] Bird L. *Nat Rev Immunol.* 2021 **21**:472. [PMID: 34183811]
[31] Kondo T *et al. Elfie.* 2023 **12**:RP88183. [PMID: 38015204]
[32] Caetano AJ *et al. Elfie.* 2023 **12**:e81525. [PMID: 36648332]
[33] Plikus MV *et al. Cell.* 2021 **184**:3852. [PMID: 34297930]
[34] Jin S *et al. Nat Commun.* 2021 **12**:1088. [PMID: 33597522]
[35] Kuang S *et al. Int J Mol Sci.* 2024 **25**:13255. [PMID: 39769019]
[36] Agrafioti P *et al. FASEB J.* 2022 **36**:e22136. [PMID: 35032412]
[37] Shen Z *et al. Sci China Life Sci.* 2024 **67**:720. [PMID: 38172357]
[38] Hajishengallis G & Lamont RJ. *Periodontol 2000.* 2021 **86**:210. [PMID: 33690950]
[39] Zhang Y *et al. Int J Oral Sci.* 2025 **17**:60. [PMCID: PMC12317052]
[40] Li J *et al. J Clin Periodontol.* 2024 **51**:1665. [PMID: 38566468]
[41] Kuang S *et al. Int J Mol Sci.* 2024 **25**:13255. [PMID: 39769019]
[42] Razzouk S. *Oral Dis.* 2024 **30**:2771. [PMID: 37794757]

Caveat Emptor is applicable among the literate community where required and possible. The publisher, its journal, editors and the internal/external reviewers take adequate steps to check, evaluate, correct, edit, revise and improve content where possible and required.