

Global Research Trends on the Links between the Oral Microbiota and Immunotherapy between 2004 and 2024: A Bibliometrics and Visualized Study

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Abstract

Background: Research over the past 21 years has shown a close relationship between oral microorganisms and immunotherapy, which has become a major focus of widespread attention in the scientific community. With the rapid increase in the number of publications in this field, it is particularly important to conduct a bibliometric analysis of related articles.

Methods: This study searched records from Web of Science Core Collection database from January 1, 2004, to December 31, 2024. By using bibliometric software CiteSpace (6.3.R1) and VOSviewer (1.6.19), co-occurrence analysis was used to count the frequency of co-occurrence of certain elements (e.g., countries, regions, institutions, etc.), cluster analysis was used to classify keywords, and burst analysis was used to identify research trends and hotspots.

Results: The number of publications in this field has shown a year-on-year increasing trend, particularly since 2018. The United States has consistently ranked first in terms of publication output. Wuhan University and Emory University are the institutions with the highest number of publications and the greatest total link strength, respectively. Journal of Immunology is the journal with the most publications in this domain. Fan M.W. and Hajishengallis are the authors with the highest number of publications and the highest total citations, respectively. Immunology is the most frequent subject category. Besides "oral microbiota" and "immunotherapy," the most popular keywords include "dendritic cells," "periodontitis," and "expression" (referring to gene/protein expression). This study is primarily focused on how the oral microbiota influences systemic anti-tumor immunity, although some effects also extend to other areas such as sublingual immunotherapy and periodontitis.

Conclusion: Over the past two decades, although a close association has been established between the oral microbiota and immunotherapy, the precise causal mechanisms remain incompletely elucidated. The translation

of theoretical discoveries into clinical practice, along with the advancement of innovative interdisciplinary research, is poised to become a prominent focal point in this field.

1. Introduction

Over the past 21 years, scholarly attention and research endeavors focused on the oral microbiome have undergone a remarkable and persistent surge¹⁻³. This surge in interest stems significantly from the recognition that the oral microbiome plays a crucial role in modulating local^{4,5} and systemic immune responses^{6,7}. Immunotherapy harnesses or modulates the body's immune system to treat disease by either enhancing its activity against pathogens/aberrant cells or suppressing pathological immune responses in autoimmune/allergic conditions^{8,9}. Emerging evidence specifically implicates the oral microbiota as a critical regulator of systemic immune responses, with its dysbiosis significantly influencing outcomes in immune checkpoint inhibitor (ICI) therapies¹⁰. Compared to immunotherapy responders, non-responders frequently exhibit distinct oral microbial signatures, characterized by enrichment of periodontal pathogens such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and reduced abundance of commensal *Streptococcus* species¹¹. Oral pathobionts can disseminate systemically, colonize tumor tissues, and promote an immunosuppressive microenvironment via activation of myeloid-derived suppressor cells (MDSCs) or modulation of regulatory T cells (Tregs)¹². Microbial metabolites, including short-chain fatty acids (SCFAs) and polyamines, further shape host immunity by altering dendritic cell function and T-cell differentiation^{13,14}. Notably, elevated salivary levels of prostaglandin E₂ (PGE₂) and interleukin-8 (IL-8), linked to periodontal dysbiosis, correlate with diminished anti-PD-1 efficacy^{14,15}.

Therapeutic strategies targeting the oral microbiome are under active investigation. Preclinical studies demonstrate that periodontal intervention or probiotic administration (e.g., *Lactobacillus reuteri*) enhances ICI responsiveness by restoring microbial homeostasis and reducing inflammation¹⁶. Fecal microbiota transplantation (FMT) from responders, which partially restores oral-gut microbial continuity, has shown promise in overcoming immunotherapy resistance¹⁷. Furthermore, microbial biomarkers such as *Veillonella parvula* and *Prevotella melaninogenica* are being explored for predicting clinical response to ICIs^{18,19}.

Interdisciplinary integration of microbiology, and immunology has increased the complexity of this knowledge domain. Despite exponential growth in publications on "oral microbiota and immunotherapy," a systematic analysis of research trends, knowledge structure, and emerging frontiers is lacking. Bibliometrics provides quantitative tools to map the evolution of scientific fields through co-citation analysis, keyword co-occurrence, and collaboration networks^{20,21}. This study employs bibliometric methods to analyze global publications from 2004 to 2024, aiming to identify core research themes, influential contributors, and future directions in oral microbiome-immunotherapy research.

2. Materials and methods

2.1. Sources of data and search strategy

In order to ensure the authority of the original documents, data were retrieved and downloaded from the Web of Science Core Collection (WoSCC). All the searches were conducted on the same day to avoid potential bias due to daily database updates. In our study, we conducted a systematic analysis of publications from January 1st, 2004,

to December 31st, 2024, to delineate the evolving landscape of oral microbiome and immunotherapy. The search strategy is illustrated in the flowchart in Figure 1.

2.2. Inclusion criteria

The inclusion criteria encompassed papers and reviews related to the search while excluding letters, newsletters, book reviews, and other nonresearch materials. The document language is limited to “English”.

2.3. Data collection and analysis

The basic information in the records, such as Publications, countries/regions and institutions, authors and co-cited authors, journals, co-cited references and keywords, were extracted and classified to analyze the data better. For some important articles, We retrieved data from the Web of Science database to extract key bibliometric indicators, including the top 10 contributing authors, countries, and institutions. Additional metrics such as H-index values, Total Citations (TC), and Impact Factor (IF) were calculated using RStudio. Partial citation data were also processed and visualized with VOSviewer. Next, we used Microsoft Excel 2020, Rstudio, VOSviewer 1.6.18 (van Eck and Waltman, 2010), Citespace 6.1.6 (Shen et al., 2019), Pajek, OriginPro, and other software tools. In the VOSviewer, the larger the nodes are, the more articles there are in that research direction, and the thicker the connecting lines are, the closer the association. In CiteSpace, centrality measures a node's significance, with larger nodes and purple outer rings denoting higher importance.

3. Results

3.1. General characteristics of the retrieved documents

According to the search strategy, a total of 953 documents were retrieved, but after screening according to the inclusion and exclusion criteria, only 834 documents could be used for further analysis (Figure 1). Of these, 621 were original, and 213 were review articles. In the past 20 years, the number of papers in this field has been increasing year by year, particularly after 2018.

3.2. Country/region and academic institution distribution

The authors of these articles were from 72 countries or regions. To date, a Chinese writer named Li has published a total of 18 articles, ranking first for the number of articles published. The authors ranked second through fifth in publication count are from Japan, France, China, and Germany respectively. Figure 2A shows the global distribution of research output in this field. In addition, we analyzed the change in trends in the annual number of publications from authors based in the countries above (Figure 2D and Table 1). For nearly two decades, the United States has maintained a leading position in publication output within the relevant field. Since 2015, the volume of publications from the US has exhibited a significant surge. Before 2019, Japan held the second position. However, over the past 10 years, China has experienced a dramatic increase in its publication count, overtaking Japan to secure the second position. (Figure 2D) Notably, over the most-recent three years (2022-2024), China's annual publication volume has consistently ranked first globally. (Figure 2C) This indicates that research on oral microbiota and immunotherapy has emerged as a prominent focus in China in recent years.

To further explore any cooperation relationship between countries/regions, we used VOSviewer software to perform a co-occurrence clustering analysis. Node size is proportional to publication output, with larger nodes indicating higher research productivity of the represented country. Colors denote categorical affiliations across six distinct organizations. (Figure 3A) The thickness of the lines indicated the strength of research cooperation between countries/regions, with thicker lines denoting stronger collaboration. As shown in Figure 3, the United States occupies a dominant position, exhibiting the highest total link strength. The collaborative ties between the U.S. and China, Brazil, and Japan are particularly strong. Ranked by node size, China and Japan hold the second and third positions for link strength, respectively. Notably, a distinct cluster (blue cluster) is formed by several European countries/regions, such as England and Sweden. The red cluster is predominantly dominated by Germany, indicating its structural centrality within this regional segment of the collaboration network.

These studies included 1,153 academic institutions, with the Emory University, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard University Medical School (HMS), University of Helsinki ranking among the top five institutions for the number of papers published. Figure 3 shows co-occurrence clustering analysis was employed to investigate collaborative relationships among leading institutions in this field. The results demonstrate that Emory University exhibits the highest total link strength, indicating its position as the most extensively connected entity within the collaboration network. Furthermore, Wuhan University and Nihon University emerged as the primary knowledge producers, generating the highest research output volume among all institutions.

3.3. Journal distribution

The 834 papers were published in 395 academic journals. As shown in Table 2, among the top 10 most productive journals, the USA and Switzerland contribute the most proportion. The average journal IF listed in Table 3 was 5.94, and their average H-index was 11.1. All the journals were classified as Q1 (the top 25% of the IF distribution).

When two or more journals are jointly cited in the same article, they are considered to form a co-citation relationship. Table 4 lists the top 10 co-citation journals, eight from the USA, two from the UK. The majority of these ten articles are considered as Q1 or Q2. We used VOSviewer software to perform a co-occurrence clustering analysis. The results showed that these co-citation publications could be divided into three clusters (Figure 4A): (1) oncology-related journals in the red cluster, such as *Annals of Oncology*, *BMC Cancer*, *Oral Oncology*, *Cancer Immunology Research*; comprehensive scientific journals in green, such as *PLOS ONE*, *PNAS*, *Nature Medicine*, *Blood*; (3) allergy and immunology-related journals in blue, such as *Allergy*, *European Journal of Immunology*, *Journal of Allergy and Clinical Immunology*, *Journal of Experimental Medicine*.

3.4. Author distribution

A total of 4,946 authors are included in these publications. Table 5 describes the top 10 most productive and co-cited authors' basic information. The higher volume of publications by Chinese researchers in the field of oral microbiota and immunotherapy reflects substantial national prioritization and resource allocation towards this domain. Nevertheless, the continued dominance of U.S.-based studies in citation metrics indicates considerable

room for China to enhance its research impact, suggesting untapped potential for future development. Fan MW of the Wuhan University in China published the most publications in this field between 2004 and 2024, followed by Abiko Y, Moingeon P, Xu QA, Novak N. When two or more publications jointly cite the works of specific authors, these authors form a co-citation relationship. Such cohorts typically demonstrate substantial research output and scholarly influence, thus establishing them as pivotal contributors and intellectual leaders within the field. Table 5 lists the top 10 co-citation authors, and Allam, J. also ranked among the top five in the high co-citation authors list, indicating that he published the greatest number of articles and had extensive international influence. Figure 4B shows a co-citation author network visualization. The node size denotes co-citation frequency, while authors clustered within the same color group demonstrate more frequent co-citation relationships, reflecting cohesive research communities.

3.5. Category analysis

The subject category represents the main research direction of a study. In general, 834 papers involved 78 WOS categories, and the top five subjects were identified as Immunology, Oncology, Dentistry Oral Surgery Medicine, Microbiology, and Medicine Research Experimental. Figure 5 presents a temporal slice analysis of disciplinary distribution, wherein node size corresponds to publication volume. The color gradient—shifting from purple to red—indicates chronological evolution, with purple representing earlier time periods and red denoting more recent years. The outer purple rings highlight nodes with high betweenness centrality, signifying their pivotal role in knowledge integration and interdisciplinary connectivity.

The disciplinary network is clustered into six distinct groups, including #0 Dentistry, Oral Surgery & Medicine, #1 Immunology, and #5 Cell Biology, among others. Notably, clusters #0, #1, and #2 exhibit strong emerging potential, as reflected in their structural prominence and recent citation activity, suggesting sustained intellectual influence and capacity for future development.

3.6. Keywords analysis

The 834 articles contained a total of 4,271 different keywords. It is noteworthy that beyond terms related to “immunotherapy” and “oral microbiota”, high-frequency keyword analysis revealed particularly prominent occurrences of terms such as "expression(gene/protein)," "periodontitis," and "dendritic cells." To elucidate the knowledge structure of this field, we conducted co-occurrence analysis using VOSviewer and Citespace software. As shown in Figure 5A, node size represents keyword frequency, while connection thickness indicates co-occurrence strength. Figure 5B categorizes the keywords into five major clusters through bibliometric clustering, labeled as squamous cell carcinoma, dental caries, porphyromonas gingivalis, rheumatoid arthritis, sublingual immunotherapy, and tumor microenvironment to denote core themes (Figure 5B). Temporal evolution analysis (Figure 6D) demonstrates the developmental trajectory of the top 25 keywords in oral microbiota and immunotherapy research from 2004 to 2024, with red zones marking burst detection periods. Longitudinal analysis indicates a significant paradigm shift in research focus: from early singular investigations of oral fundamentals to studies exploring oral-immunotherapy connections, with recent years showing concentrated attention on the mechanistic interplay between oral microbiota and cancer immunotherapy.

3.7. Reference analysis

When two or more publications are jointly cited by an article, they constitute a co-citation relationship. Such frequently co-cited literature is regarded as a critical knowledge foundation in the field. Using RStudio, we identified the top 10 most frequently co-cited articles, which were published in *The Lancet* (3 articles)²²⁻²⁴, *Journal of Allergy and Clinical Immunology* (2 articles)^{25,26}, *Allergy* (2 articles)^{27,28}, *mBio* (2 articles)^{29,30}, and *The New England Journal of Medicine* (1 article)³¹. These publications span three major research domains: cancer immunotherapy (head and neck cancer, liver cancer), allergic immunotherapy (pollen allergens), and oral microbiology (dental caries, periodontal diseases), all representing high-impact studies in their respective fields. Specifically, four articles focus on cancer immunotherapy, three investigate oral mucosal immunity and allergic immune mechanisms, and another three explore the relationship between oral microbiota and diseases. Furthermore, all cited references were divided into five distinct clusters. The red cluster primarily encompasses studies on immunotherapy for head and neck cancer. The yellow cluster is predominantly associated with infection immunity and its relationship with oral health. The blue cluster focuses on fundamental research related to oral microbiota and vaccine development.³² The purple cluster centers on tumor microbiome, finally the green cluster mainly includes research on allergy treatment. (Figure 7).

3.8. Key articles in this field

We selected the top 10 articles based on the number of citations. However, article citations are greatly affected by publication time. The citation times of articles published in recent 5 years are relatively low, even in important research articles. Therefore we used the “burst terms” function of CiteSpace to analyze the references with a sudden increase in citations in nearly 5 years. We have listed the basic information of the top 9 papers with the highest burst strength.

Research on the oral microbiome's role in cancer, particularly head and neck or gastrointestinal cancers, has intensified over the past decade according to the above 19 landmark studies in this field. Landmark studies have focused on microbial dysbiosis, mechanistic links to carcinogenesis, and translational applications.

The foundational work by Pushalkar et al. (2018)³³ established a pivotal link between the oral microbiome and pancreatic ductal adenocarcinoma (PDAC). Their study revealed that PDAC tumors harbor a distinct microbiome dominated by *Fusobacterium* and other oral pathogens, which promotes immunosuppression and tumor progression by inhibiting T-cell activation and inducing M2 macrophage polarization. This work, cited 972 times, highlighted microbial ablation as a potential therapeutic strategy and spurred investigations into microbiome-based diagnostics.

Complementing this, Ferris et al.³¹ demonstrated the clinical efficacy of immune checkpoint blockade in recurrent head and neck squamous cell carcinoma (HNSCC), reporting durable responses and survival benefits with anti-PD-1 therapy. Published in the *New England Journal of Medicine*, this seminal work (citation burst: 10.27) catalyzed research into how the microbiome modulates immunotherapy responses. Subsequent studies, such as Routy et al.¹⁰, expanded this paradigm by linking gut microbiome composition to anti-PD-1 efficacy across cancers.

Recent advances emphasize early detection. Qing et al.³⁴ identified salivary microbial signatures (e.g., *Fusobacterium nucleatum*, *Porphyromonas gingivalis*) as non-invasive biomarkers for oral squamous cell carcinoma (OSCC) risk stratification. Their high-impact study, with an exceptional citation rate of 99.0 per year, underscores the translational potential of microbiome profiling in liquid biopsies.

Mechanistic insights have been further elucidated by Cohen et al.²³, who explored microbial influences on tumor immune microenvironments, and Lawrence et al.³⁵, whose genomic analyses revealed mutational signatures associated with microbial-driven inflammation.

Collectively, these studies underscore three emerging themes: (1) the pro-carcinogenic role of oral pathobionts in PDAC/HNSCC; (2) microbial modulation of immunotherapy efficacy; and (3) microbiome-based diagnostics for early cancer detection. Future efforts must prioritize clinical validation of microbial biomarkers and targeted interventions to disrupt tumor-microbiome crosstalk.

4. Discussion

4.1. Research overview

This study conducted a bibliometric analysis of publications focusing on the relationship between oral microbiota and immunotherapy from 2004 to 2024. Utilizing scientific mapping techniques, we quantitatively evaluated the geographic distribution of research outputs, core journal contributions, collaborative networks among leading authors, and the evolutionary trajectory of research themes. Through co-word analysis and examination of highly cited literature, we elucidated current research hotspots and emerging trends. Notably, the absence of prior bibliometric studies specifically addressing the intersection of oral microbiome and immunotherapy underscores the significant academic value and promising development potential of this research field.

The following reasons may explain why the oral microbiome has gradually become a hotspot in immunology research. Firstly, the recognition of the oral cavity as a critical interface for systemic inflammation and immune modulation has reshaped traditional cancer etiology models.³⁶ Compared with studying isolated oncogenic pathways, scientists increasingly focus on the complex interplay between microbial communities, host immunity, and epithelial carcinogenesis^{23,31,37}. With advancing research, the oral microbiome—once considered merely a passive bystander—is now recognized as an active contributor to tumorigenesis through chronic inflammation, DNA damage, and immune evasion.^{11,33} The urgent need for early cancer detection and novel therapies has accelerated the development of specialized technologies. For example, high-resolution metagenomic sequencing, spatial transcriptomics, and germ-free murine models now enable precise characterization of oral microbial dysbiosis and its functional impact on tumor microenvironments.^{35,38-40} In addition, substantial governmental investment provides foundational support for sustained innovation. Initiatives like the U.S. National Institute of Dental and Craniofacial Research's (NIDCR) Oral Microbiome and Systemic Disease program, the European Union's MetaCardis consortium, and China's Oral Microbiome Genome Project have collectively allocated over \$500 million to elucidate oral microbiome-cancer linkages^{10,41} (NIDCR Strategic Plan 2021–2026;). These efforts drive interdisciplinary convergence across microbiology, immunology, and precision oncology.

4.2. Characteristics of publications

Over the past two decades, the United States has consistently maintained a leading position in the total volume of publications in this field. However, since 2015, China has demonstrated a remarkable surge in its annual publication output, surpassing all other countries in yearly production after 2022 and securing the top position globally. In terms of total national citation count, the United States ranks first, followed closely by China in second place. It is noteworthy that European nations, such as the United Kingdom and France, although producing a relatively smaller number of publications, exhibit significantly higher average citation rates per article. This indicates that their research findings garner substantial academic influence and attract considerable attention.

At the institutional level, analysis reveals that Wuhan University and Japan University rank first and second globally in the number of publications. However, when assessing the total link strength—a metric indicative of collaborative influence and research impact—Dana-Farber Cancer Institute and Brigham and Women's Hospital emerge as the top two institutions worldwide. These two institutions also rank fourth and sixth, respectively, in the list of most cited publications, further solidifying the leadership of U.S. institutions in driving cutting-edge research within this domain. Concurrently, the prominent output from East Asian institutions highlights the considerable potential and growing influence of this region in scientific research.

4.3. Development trend and research hotspots

The research focus on the association between oral microbiota and immunotherapy primarily centers on how oral microbiota influences systemic anti-tumor immunity. A primary mechanism is the systemic dissemination of oral pathobionts. Certain periodontal pathogens, such as *Fusobacterium nucleatum* (Fn) and *Porphyromonas gingivalis* (Pg), can translocate from oral niches like periodontitis into the systemic circulation via transient bacteremia or through swallowing and subsequent gut colonization.⁴²⁻⁴⁴ This ectopic colonization can compromise intestinal barrier integrity, potentially initiating or exacerbating a state of chronic, low-grade systemic inflammation^{6,45,46}. Crucially, these bacteria can infiltrate and colonize tumor tissues themselves, where they contribute to shaping an immunosuppressive tumor microenvironment (TME). This is achieved by recruiting myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)^{47,48}, and through the activation of novel immune checkpoints like TIGIT^{49,50}, thereby dampening the host's anti-tumor immune response and diminishing the effectiveness of immunotherapies.^{51,52}

Co-citation analysis of the current literature reveals that research in this field is rapidly evolving from establishing correlative links to validating causal relationships and pursuing clinical applications.⁵³ The research community is moving beyond merely acknowledging the association between oral microbiota and immunotherapy outcomes; the focus has now shifted towards developing innovative strategies to therapeutically manipulate the oral microbiome to improve cancer patient prognosis.^{54,55} This endeavor represents a significant opportunity for collaboration between oral medicine and oncology.⁵⁶

Although the primary research focus remains on oncology, the immunomodulatory role of the oral microbiome extends to other therapeutic areas:

The efficacy of Sublingual Immunotherapy (SLIT) for allergies is believed to be mediated by the induction of immune tolerance at the oral mucosal interface. Emerging evidence suggests that the oral microbiota acts as a key regulator in this process, likely by influencing the local immune milieu and antigen-presenting cell function,⁴¹ though specific studies directly linking specific oral taxa to SLIT efficacy are still expanding.

Investigations into the relationship between oral dysbiosis (e.g., periodontitis) and conditions like Rheumatoid Arthritis (RA) are ongoing. The proposed mechanisms involve the activation of systemic inflammation and molecular mimicry. A prominent hypothesis involves the enzyme peptidylarginine deiminase (PAD) produced by periodontal pathogens like *P. gingivalis*, which catalyzes the citrullination of host proteins.^{57,58} These citrullinated peptides can break immune tolerance, triggering the production of anti-citrullinated protein antibodies (ACPAs), a hallmark of RA.⁵⁷⁻⁶¹

4.4. Limitations and future research directions

In this study, our analysis was limited to publications indexed in the Web of Science and included only English-language literature, which may have led to the omission of relevant studies published in other languages or databases. Moving forward, several key research directions deserve further attention. First, the causal relationship between the oral microbiota and immunotherapy efficacy remains to be firmly established, which is critical for developing targeted microbial interventions. Second, although oral microbiota-based biomarkers hold promise for predicting immunotherapy response and enabling personalized treatment strategies, their clinical utility still requires validation through large-scale, high-quality randomized controlled trials. Lastly, standardized protocols for oral microbiome sampling, sequencing, and bioinformatics processing, as well as clinical guidelines for modulating the oral microbiota, are urgently needed to facilitate translation into practice.

5. Conclusion

In summary, research on the correlation between the oral microbiota and immunotherapy has emerged as a prominent field in recent years, with a consistent annual increase in the number of related publications. Bibliometric analysis reveals that the United States and Wuhan University are the most productive country and institution, respectively. The Journal of Immunology has published the most articles in this domain, with Fan M.W. being the most prolific author. Hajishengallis, George, is a key contributor to the most cited publication. "Immunotherapy" and "Oncology" represent the most frequent subject categories. The following keywords signify current research frontiers: dental caries, sublingual immunotherapy, and tumor microenvironment. Future research will likely place greater emphasis on the clinical translation of theoretical findings and innovative interdisciplinary investigations.

Data availability statement

The original contributions presented in this study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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