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Short Communication

A scientometric study on methylation modification and identification of related genes in oral potentially malignant disorders and oral cancer

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Abstract *Background/purpose:* Accumulating evidence indicates that methylation modification alterations involve in the development and progression of oral cancer. The purpose of this study was to analyze the scientometric characteristics of methylation modification in oral potentially malignant disorders (OPMD) and oral squamous cell carcinoma (OSCC).
Materials and methods: All the papers on methylation research in OPMD/OSCC were comprehensively retrieved from the Scopus database with emphasis on the identification of methylation related genes.
Results: A total of 365 papers on methylation research in OPMD/OSCC were retrieved. The total citation count was 9998 and the *h* index was 53 for all the papers. The common keywords included prognosis, sensitivity and specificity, smoking, cohort analysis, saliva, receiver operating characteristic, follow up, risk factor, cancer diagnosis, tumor suppressor gene, biological marker. Among the 365 papers, a total of 542 methylated genes and 65 microRNAs were identified. The most common methylated gene was p16, followed by MGMT, DAPK/DAPK1, E-

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cadherin, RASSF1/RASSF1A, KIF1A, TIMP3, RUNX3, LINE1, CDH1, TERT, ZAP70, FLI1, GP1BB, and ZNF582. The most frequent methylation related microRNA was miR-296, followed by miR-193 and miR-137.
Conclusion: This study for the first time elucidated the scientometric characteristics of all the publications on methylation modification in oral carcinogenesis, and would provide new insights for researchers to comprehend the methylation specific gene profile related OPMD/OSCC.

Introduction

Oral potentially malignant disorders (OPMD) and oral squamous cell carcinoma (OSCC) are a series of oral diseases often undergo transformation from epithelial hyperplasia, various degrees of epithelial dysplasia, to carcinoma.[1,2] Oral carcinogenesis is a typical multistep process with stepwise accumulation of genetic and epigenetic alterations.[3] DNA/RNA methylation modification as one of epigenetic alterations affect gene expression and cellular behavior through epigenetic mechanisms, which is recognized to play a crucial role in oral carcinogenesis.[4–6] Identification of specific methylation pattern is emerging as biomarkers for early detection of oral cancer and patients' prognosis, and is crucial for the development of targeted therapies.[4] Therefore, it is promising to develop novel methods for screening and therapy for the management of OPMD/OSCC by comprehending and addressing the methylation modification.

Considering the important biological processes in oral carcinogenesis, methylation modifications of the oncogenes and tumor suppressor genes offer prospective targets for diagnostic and treatment approaches.[7] Scientometrics is a useful tool that utilizes citation and bibliometric data to measure scientific output and research trend of a specific research field.[8–10] The previous bibliometric analyses of RNA methylation in some fields of cancer have been reported,[11,12] but a similar analysis of methylation modification in oral cancer is lacking. Such analysis would be important for understanding the research output and hotspots of this field and guiding future research directions. Hence, the purpose of the current study was to analyze the scientometric characteristics of methylation modification in OPMD/OSCC research with emphasis on the identification of methylation related genes, so as to give inspiration and strategies of basic and clinical research in this field.

Materials and methods

As per the methodology described previously,[8–10] All the papers on methylation research in OPMD/OSCC were comprehensively retrieved from the Scopus database on 12 July 2025. According to the search strategy described in supplementary Table S1, we used medical subject terms "methylat* OR hypermethylat* OR hypomethylat*" in the title AND "OPMD or OSCC" and their synonyms in the title/abstract/keywords in literature search. The asterisk indicates a wildcard used to search for all endings including fifth or more root words. The scientometric characteristics of all the eligible papers were recorded for the following information: title, keyword, citation count, publication year, journal of publication, article type, authorship, affiliation, and country/region of origin. Data search and extraction were performed independently by two investigators, and any discrepancy of results was resolved in a consensus symposium. Microsoft Office Excel 365 was used for index model building, and the Bibliometrix Biblioshiny R-package software was used for bibliometric statistics. In this descriptive study, variables were presented as numbers and percentages. No comparisons were made, and thus no *P*-values were set.

Results

Citation characteristics

With the search strategy algorithm, a total of 365 papers on methylation research in the field of OPMD/OSCC were retrieved in the Scopus database. Of these, 93 (25.5 %) papers involved in OPMD research. As for type of papers (Fig. 1A), the most type of papers on methylation research in OPMD/OSCC was article (n = 326), followed by review (n = 19) and letter (n = 8). The total citation count (after removal of self-citations) was 9998 (9132) and the *h* index was 53 (50) for all the papers. To further concretize the trends of scientific output, we assessed the annual number and accumulated citations of the papers during 2005–2024 (Fig. 1B). The annual number of the papers stably raised from 7 to 35 during 2005–2024. The accumulated citations (after removal of self-citations) of the papers steadily increased from 75 (70) to 767 (689) during 2005–2024. The detailed information on publication year, authors, title, keywords, abstract, journal of publication, citation count, institutions, and paper type of all the papers methylation research in OPMD/OSCC on are presented in supplementary Tables S2.

Bibliometric characteristics

Fig. 1C displays cloud graphs of journals of publications, contributing authors, institutions, and countries/regions of origin of the papers on methylation research in OPMD/OSCC. The journal with largest number is *Oral Oncology* (n = 29), followed by *Oral Diseases* (n = 14) and *Journal of Oral Pathology and Medicine* (n = 13). The contributing

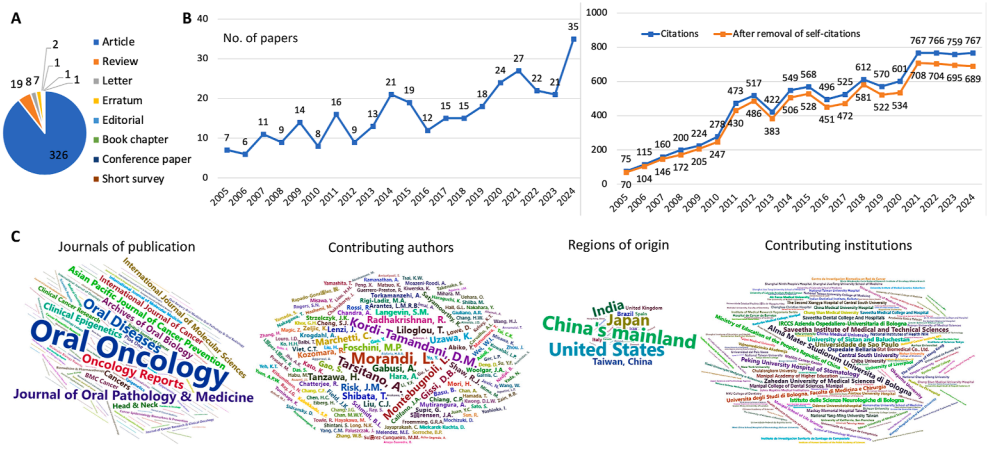

Figure 1 Bibliometric characteristics of the papers on methylation research in the field of OPMD/OSCC. (**A**) The numbers of different paper types. (**B**) The annual number and accumulated citations of the papers during 2005—2024. (**C**) Cloud graphs of journal of publication, contributing authors, regions and institutions of origin. The font size indicates the number of papers; a larger size means more papers in the cloud graphs.

author with largest number of papers is Morandi, L. (n = 10), followed by Kordi-Tamandani, D.M. and Tarsitano, A. (both n = 8). The contributing institution of origin with the maximum number is Alma Mater Studiorum Università di Bologna (n = 471), followed by Universidade de São Paulo and Saveetha Institute of Medical and Technical Sciences (both n = 9). The contributing region of origin with the largest number is China's mainland (n = 65), followed by United States (n = 62) and Japan (n = 53).

Research characteristics

Based on the frequency of the main keywords in all the papers on methylation research in OPMD/OSCC (Fig. 2A), a list of the common keywords is automatically recognized by the database, respectively. The most common study design was controlled study, followed by major clinical study and cell line in vitro study. The most frequent experiment method was polymerase chain reaction, followed by immunohistochemistry and cell proliferation test. The common keywords of clinical study aspect included prognosis, cancer staging, sensitivity and specificity, smoking, cohort analysis, saliva, overall survival, lymph node metastasis, receiver operating characteristic, follow up, risk factor, cancer diagnosis, survival analysis, and decitabine. The common keywords of bioresearch aspect included pathology, genetics, metabolism, gene expression, tumor suppressor gene, protein expression, gene silencing, biological marker, hypermethylation, genetic association, p16, cyclin dependent kinase inhibitor 2A (CDKN2A), Cadherins, death associated protein kinase (DAPK), microRNA, and microarray analysis.

Identification of methylated genes

We highlighted the identification of methylation related genes, which can reflect the gene profile of methylation research in OPMD/OSCC. Among the 365 papers, a total of 542 methylation related genes and 65 microRNAs were identified. Of these, 129 methylation related genes and 9 microRNAs were occurred in more than one paper (Fig. 2B). The most frequent methylation related gene was p16 occurred in 58 papers, followed by MGMT in 32 papers, DAPK/DAPK1 in 28 papers, E-cadherin in 18 papers, RASSF1/

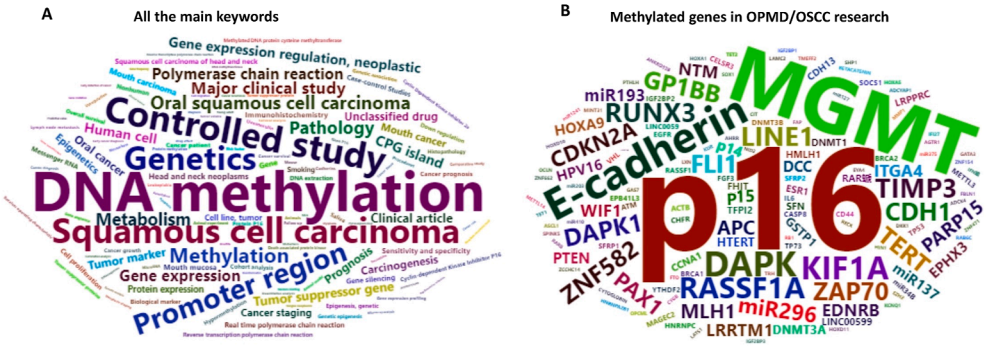

Figure 2 Research characteristics of the papers on methylation research in the field of OPMD/OSCC. (**A**) Cloud graph of all the main keywords. (**B**) Cloud graphs of methylated genes. The font size indicates the number of papers; a larger size means more papers in the cloud graphs.

RASSF1A in 15 papers, and KIF1A in 13 papers. Besides, TIMP3, RUNX3, LINE1, CDH1, TERT, ZAP70, FLI1, GP1BB, and ZNF582 were occurred in more than 10 papers on methylation research in OPMD/OSCC. On the other side, the most frequent methylation related microRNA was miR-296 occurred in 9 papers, followed by miR-193 in 7 papers and miR-137 in 6 papers. Then, the common critical genes were identified from the papers on methylation research in OPMD/OSCC.

Discussion

Methylation modification, which studies genetic modification in gene expression without altering the sequence of nucleic acid, is crucial for understanding oral carcinogenesis.[4] The development and progression of OPMD/OSCC are significantly influenced by both hypermethylation and hypomethylation.[7] This scientometric study attempted to analyze the bibliometric characteristics and research trends of all the papers on methylation research in OPMD/OSCC retrieved from the Scopus database. The increasing numbers and citations of these papers each year suggest that the issue has governed increasing attention and investigation. It could be speculated that the numbers and citations will continue to grow in the coming years. Bibliometric items in sequence would aid clinicians and researchers in choosing target journals, finding potential collaborators or partner institutions, as well as promoting mutual understanding and more reciprocal cooperation.

The strength of this study was to identify gene profile of methylation research in OPMD/OSCC (Fig. 2B). We confirmed that DNA methylation is among the most frequently studied epigenetic changes in oral carcinogenesis.[13—15] DNA hypermethylation often leads to tumor suppressor genes, such as p16, MGMT, DAPK, TIMP3, APC, and CDH1 inactivation and hypomethylation often leads to proto-oncogenes, such as EGFR, PTHLH, and LINE1, promoting oral cancer development.[7] The differentially methylated genes involved in OSCC encompass a broad spectrum of cellular processes, including cell cycle (e.g. p16, p15, BRCA1), DNA repair (e.g. MGMT, BRCA1), and apoptosis (e.g. DAPK, RASSF1), and most of them are hypermethylated. Oral dysplasia and lichen planus with hypermethylated p16 and ZNF582 were associated with increased risk of malignant transformation.[16—19] Significantly, DNA methylation in saliva and oral swabs was reported to be a promising non- and minimally invasive tool for OPMD/OSCC diagnosis.[20—22] Besides, RNA methylation, mainly N6-methyladenosine (m6A) methylation, is also emerging as one of key epigenetic modifications plays a critical role in OPMD/OSCC.[6,23]

Methylation modification of specific gene profile can be a reference for the treatment of OPMD/OSCC, since it is a promising adjuvant therapeutic target for oral carcinogenesis. Agents like histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors demonstrate the potential for reversing aberrant epigenetic patterns, perhaps reactivating silenced tumor suppressor genes and suppressing oncogenes.[4,7] However, these inhibitors have apparent toxicity and side effects, and some even decrease the efficacy of other chemotherapy drugs when used in combination.[4,7] To improve therapeutic effect, more targeted DNMT and HDAC inhibitors as well as additional epigenetic medications should be developed.[24] There were also natural compounds reported to inhibit DNA methylation. Among them, epigallocatechin gallate (EGCG), an active phenolic compound of green tea was reported to serve as a DNA demethylating agent, could reactivate epigenetically silenced tumor suppressors to inhibit the growth of OSCC cells.[25] Nevertheless, the most of studies are limited to detecting abnormal methylation phenotypes, and further research on molecule mechanism is needed.

In summary, the current study for the first time elucidated the scientometric characteristics of all the papers on methylation modification in OPMD/OSCC. This scientometric study would help in improving in investigations on methylation modification in oral carcinogenesis, and provide new insights for researchers to comprehend the methylation specific gene profile related OPMD/OSCC.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2025.07.024.

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