Journal of Dental Sciences 20 (2025) 2483–2488

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Short Communication

A scientometric study on Wnt and Notch signaling pathways in oral potentially malignant disorders and oral cancer

Xiaoliang Luo [a], Yiwen Deng [b,c**], Hao Wu [a*]

[a] *Department of Periodontology and Oral Mucosa, Changsha Stomatological Hospital, School of Dental Medicine, Hunan University of Chinese Medicine, Changsha, Hunan, China*
[b] *Department of Oral Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[c] *College of Stomatology, Shanghai Jiao Tong University, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Shanghai Key Laboratory of Stomatology, Shanghai Research Institute of Stomatology, Shanghai, China*

Received 7 June 2025; Final revision received 12 June 2025
Available online 27 June 2025

KEYWORDS
Bibliometrics;
Oral cancer;
Oral potentially malignant disorders;
Molecular mechanisms;
Notch;
Wnt/β-catenin

Abstract *Background/purpose:* Accumulating evidence indicates that aberrant activation of certain cellular signaling pathways occurs during the development and progression of oral cancer. The purpose of this study was to analyze the scientometric characteristics of Wnt and Notch pathways in oral potentially malignant disorders (OPMD) and oral squamous cell carcinoma (OSCC).
Materials and methods: All the papers on Wnt and Notch pathways in OPMD/OSCC were comprehensively retrieved from the Scopus database.
Results: A total of 301 and 169 papers on Wnt and Notch signaling pathway in the field of OPMD/OSCC were retrieved, respectively. As for Wnt pathway in OPMD/OSCC research, distinctive keywords included canonical Wnt signaling, β-catenin, CTNNB1 protein, cyclin D1, frizzled protein, Myc, Bcl-2, transcription factor, DNA methylation, long noncoding RNA, and microRNA. As for Notch pathway, distinctive keywords of bioresearch aspect included cancer stem cell, angiogenesis, genetic association, oncogene, and Jagged1. There were the same common keywords of bioresearch aspect, such as metabolism, genetics, signal transduction, apoptosis, cell proliferation, carcinogenesis, tumor marker, epithelial mesenchymal transition, protein function, drug screening, and gene mutation.

* Corresponding author. Department of Periodontology and Oral Mucosa, Changsha Stomatological Hospital, Hunan University of Chinese Medicine, 389 Youyi Road, Changsha, Hunan 410005, China.
** Corresponding author. Department of Oral Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, 500 Quxi Road, Shanghai 200011, China.
E-mail addresses: sunny3311@sina.com (Y. Deng), 30093444@qq.com (H. Wu).

https://doi.org/10.1016/j.jds.2025.06.015

Conclusion: This study for the first time elucidated the scientometric characteristics of all the publications on Wnt and Notch pathways in OPMD/OSCC, and would provide new insights for researchers to delve into the mechanisms of Wnt and Notch related OPMD/OSCC and translate into clinical studies.

Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 90 % of oral cancers, and oral potentially malignant disorders (OPMD) describe a recognizable group of oral mucosal diseases that have a significantly increased risk of progressing to OSCC.[1] Accumulating evidence indicates that aberrant activation of certain cellular signaling pathways, such as Wnt and Notch pathways, occur during the development and progression of OSCC.[2,3] Wnt and Notch signaling are two important pathways that determines cell fate, and have been extensively involved in tumorigenesis and cancer progression. They as oncogenic pathways can lead to the dysregulation of cell proliferation, cycle, differentiation, and apoptosis, thus causing the malignant transformation of cells and ultimately causing oral carcinogenesis.[2,3] Studying the signaling pathways that play roles in oral carcinogenesis, tumor progression, invasion and metastasis is critical in the understanding of the process and in determining molecular targets against OSCC. In general, in-depth understanding of the Wnt and Notch pathways will help us to elucidate the molecular mechanisms and provide insights for the treatment of oral cancer.

Two earlier review articles published in the same issue (volume 97, No. 6) of *Journal of Dental Research* summarized seminal discoveries and advances in Wnt and Notch pathways in head and neck squamous cell carcinoma.[4,5] Recent years, increasing papers on Wnt and Notch-related OPMD/OSCC research have accumulated rapidly and received extensive attention.[2,3] Scientometrics is a useful tool that utilizes citation and bibliometric data to measure scientific output and research trend of a specific research field.[6–8] The previous bibliometric analyses of Wnt and Notch pathways have been applied in some fields, such as Wnt signaling in bone and liver diseases and Notch signaling in pan-cancer.[9–11] To our knowledge, a scientometric/bibliometric analysis of the two pathways in OPMD/OSCC is still lacking. Such analysis would be important for understanding the research output and hotspots of this field and guiding future research directions. Therefore, the purpose of this study was to analyze the scientometric characteristics of Wnt and Notch signaling pathways in OPMD/OSCC, so as to give inspiration and strategies of basic and clinical research in this field.

Materials and methods

As per the methodology described previously,[6–8] All the papers on Wnt and Notch pathways in OPMD/OSCC were comprehensively retrieved from the Scopus database on 22 May 2025. According to the search strategy described in Supplementary Table S1, we used medical subject terms "Wnt OR Notch" in the title AND OPMD or OSCC and their synonyms in the title/abstract/keywords in literature search. 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 301 and 169 papers on Wnt and Notch signaling pathway in the field of OPMD/OSCC were retrieved in the Scopus database, respectively. There were 48 (15.9 %) of 301 papers on Wnt involved in OPMD research, and there were 23 (13.6 %) of 169 papers on Wnt involved in OPMD research. Meanwhile, there were 7 papers on both Wnt and Notch involved in the same paper. As for type of papers (Fig. 1A), there were 249 articles and 30 reviews on Wnt pathways, and there were 145 articles and 12 reviews on Notch pathways in OPMD/OSCC. The total citation count was 9914 and the *h* index was 51 for the papers on Wnt pathways in OPMD/OSCC, and the total count was 4480 and the *h* index was 36 for the papers on Notch pathways in OPMD/OSCC.

To further concretize the trends of scientific output, we assessed the annual number and accumulated citations of the papers from 2005 to 2024 (Fig. 1B). The annual number of the papers on Wnt pathways in OPMD/OSCC ranged from 3 to 27, and the accumulated citations of the papers increased from 70 to 1193 during 2005—2024. The annual number of the papers on Notch pathways in OPMD/OSCC ranged from 0 to 16, and the accumulated citations of the papers increased from 0 to 527 during this period. Table S2 and Table S3 presents the detailed information on publication year, authors, title, abstract, journal of publication, article type, citation count, institutions, and keywords of all the papers on Wnt and Notch pathway in OPMD/OSCC, respectively.

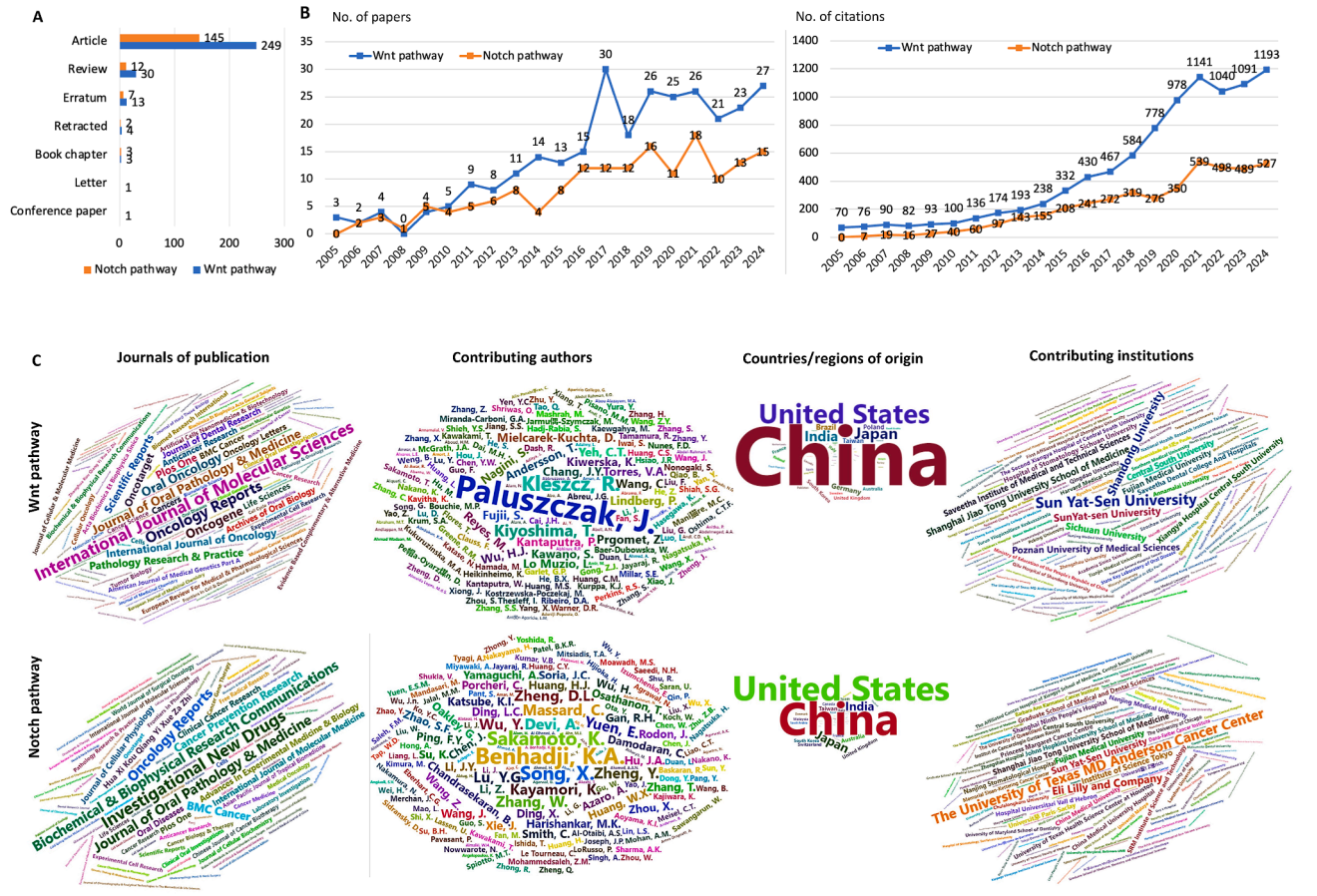

Figure 1 Bibliometric characteristics of the papers on Wnt and Notch signaling pathway in the field of OPMD/OSCC. (**A**) The numbers of different paper types. (**B**) The annual number and accumulated citations of the papers during 2005–2024. (**C**) Cloud graphs of journal of publication, contributing authors, countries and institutions of origin regarding furcation involvement publications. The font size indicates the number of papers; a larger size means more papers in the cloud graphs.

Bibliometric characteristics

Fig. 1C displays cloud graphs of journals of publications, contributing authors, institutions, and countries/regions of origin of the papers on Wnt and Notch pathways in OPMD/OSCC. As for Wnt pathways, the journal of publication, contributing author, institution and country of origin with largest number of papers was *International Journal of Molecular Sciences* (8 papers), Paluszczak, J. (8 papers), Sun Yat-Sen University (13 papers) and China (138 papers), respectively. As for Notch pathways, the journal of publication, contributing author, institution and country of origin with maximum number was *Investigational New Drugs* (6 papers), Benhadji, K.A. (6 papers), The University of Texas MD Anderson Cancer Center (9 papers) and China (63 papers), respectively. Supplementary Table S4 presents the journals, contributing authors, institutions, and countries/regions with largest number of papers (rank, 1–10).

Research characteristics

Based on the frequency of the main keywords in all the papers on Wnt and Notch pathways in OPMD/OSCC (Fig. 2A), a list of the common keywords is automatically recognized by the database, respectively. For the two pathways in OPMD/OSCC research, the most common study design was controlled study, followed by in vitro study and in vivo study. There were the same common keywords of bioresearch aspect, such as metabolism, genetics, signal transduction, pathology, protein expression, apoptosis, gene expression regulation, cell proliferation, carcinogenesis, tumor marker, epithelial mesenchymal transition (EMT), antineoplastic activity, protein function, drug screening, and gene mutation. Moreover, there were the same common keywords of experimental aspect, such as western blotting, animal experiment, immunohistochemistry, Cal-27 cell line, cell migration, cell motion, cell viability, real time polymerase chain reaction, flow cytometry, small interfering RNA, tumor growth, and cell growth.

We highlighted the analysis of distinctive research keywords, which can reflect the directions and concerned topics of research. As for Wnt pathway in OPMD/OSCC research, distinctive keywords included canonical Wnt signaling, β-catenin, CTNNB1 protein, cyclin D1, frizzled protein, glycogen synthase kinase 3alpha/3beta, intercellular signaling peptides and proteins, Myc protein, Bcl-2, transcription factor, protein phosphorylation, DNA methylation, long untranslated RNA, long noncoding RNA, and

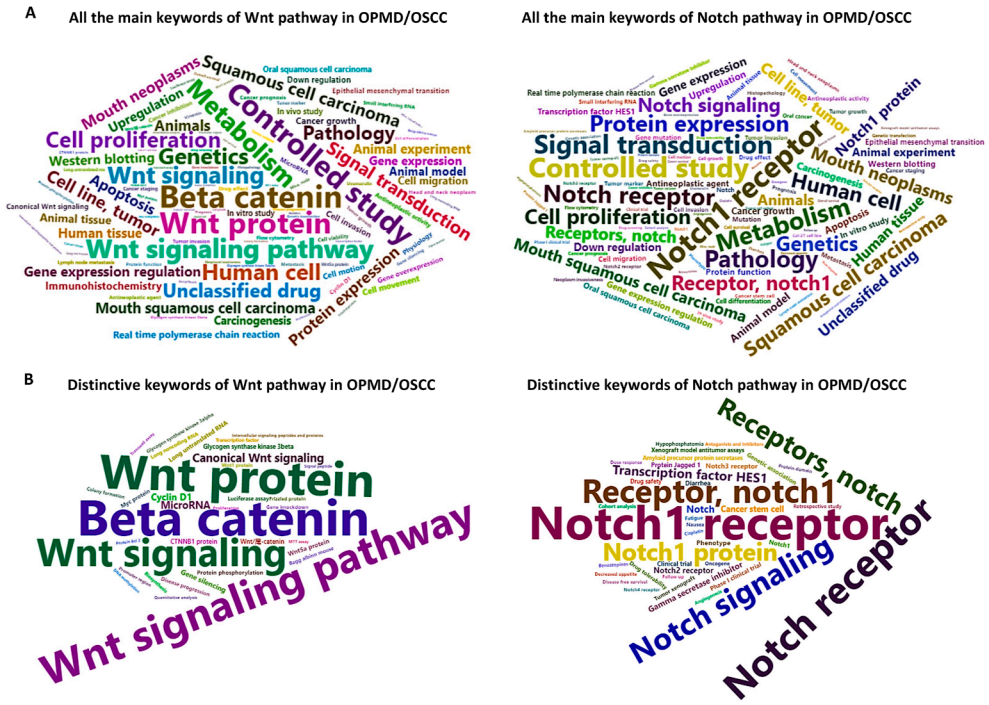

Figure 2 Research characteristics of the papers on Wnt and Notch signaling pathway in the field of OPMD/OSCC. (**A**) Cloud graph of all the main keywords. (**B**) Cloud graphs of distinctive keywords of papers. The font size indicates the number of papers; a larger size means more papers in the cloud graphs.

microRNA. Also, distinctive keywords of experimental aspect included colony formation, MTT assay, gene knockdown, gene silencing, transwell assay, and luciferase assay. As for Notch pathway in OPMD/OSCC research, distinctive keywords of bioresearch aspect included cancer stem cell, angiogenesis, genetic association, oncogene, amyloid precursor protein secretases, antagonists and inhibitors, gamma secretase inhibitor, protein domain, protein Jagged1, transcription factor HES1, tumor xenograft, and xenograft model. Notably, the keywords of clinical study aspect included cohort analysis, retrospective study, clinical trial, phase I clinical trial, follow up, dose response, decreased appetite, diarrhea, fatigue, nausea, drug safety, drug tolerability, and cisplatin.

Discussion

To explore novel avenues for the development of innovative therapeutic strategies against oral carcinogenesis, it is imperative to study the basic oral oncogenic signaling pathways and related molecules. In this respect, inhibition of crucial molecules within clinically relevant oncogenic pathways will be important. This scientometric study attempted to analyze the bibliometric characteristics and research trends of all the publications on Wnt and Notch pathways 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. The strength of this scientometric study was to highlight the analysis of the keywords that can reflect research directions and topics of concern (Fig. 2).

The canonical and non-canonical pathways are two types of Wnt signaling. β-catenin is the central component of canonical pathway. Frizzled protein is the Wnt ligands binding receptor.[2,4] The involvement of the Wnt pathway in oral carcinogenesis occurs through cell proliferation upregulation, apoptosis inhibition, initiation of EMT activation, genetic mutation, epigenetic alteration, and local invasiveness activation mechanisms.[2,4] Furthermore, several Wnt molecules with potential pharacological value are being explored for future therapeutic interventions.[12–16] For instance, Wnt5a expression was found to be increasing from normal oral mucosa to oral epithelial dysplasia and OSCC, and it expression increased along with increasing grade of dysplasia, and the highest expression was detected in OSCC.[14,15] Moreover, Wnt5a expression was statistically associated with lymph node metastasis of OSCC.[16] These outcomes offer an opportunity for Wnt5a which could be used as a potential biological marker for oral carcinogenesis.

Notch signaling pathway mainly contains Notch receptor (NOTCH1-4), ligands (e.g. Jagged1 and 2), binding proteins, and downstream target genes.[5] A relationship between mutations in Notch pathway and CD8 T+ cell infiltration via PD-L1 expression suggested it leading to enhanced antitumor immunity.[17] Knockdown of Notch suppressed EMT and induced angiogenesis in oral submucous fibrosis (OSF) by regulating TGF-β1, suggesting that the Notch-TGF-β1 pathway may serve as a therapeutic intervention target for OSF.[18] The oncogenic role of NOTCH1 in oral lichen planus and OSCC was investigated, suggested NOTCH1 as a

biomarker for the assessment of the tumorigenesis process with a definition of a standard threshold for potentially malignant lesions and malignant tumors.[19] Future research trends in this area include safety and targeting studies on monoclonal antibodies and small molecules, potential target drugs and clinical trials for the treatment of OSCC.[20] Compared with Wnt pathway, dysregulation of the Notch pathway is a topic with more potential for further translation to clinical research.

The crosstalk of Wnt and Notch pathways during oral carcinogenesis seems to be a rational approach for the development of potential therapeutic regimens. OSCC harbor inactivating mutations in NOTCH1, which are associated with enhanced β-catenin activity.[21] Notch crosstalk with the Wnt pathway has provided intricate insights in cancer stemness maintenance and malignant behaviors in OSCC.[22] Using combinations of drugs that individually target each pathway or repurposing available drugs, designing multi-target drugs against these pathways may be practical therapeutic approach. Indeed, this combined targeted therapy shows more satisfactory results when compared with single therapy in multiple cancer conditions.[21] The development and well-defined combinatorial application of small molecule inhibitors, monoclonal antibodies and/or alternative treatment strategies at specific stages of OSCC development should be articulated for obtaining enhanced treatment efficacies and clinically meaningful results. Therefore, comprehensive knowledge of the impact of key regulatory molecules in the development and progression of OSCC is expected to provide novel options for the treatment of this highly aggressive malignancy.

In summary, this study for the first time elucidated the scientometric characteristics of all the publications on Wnt and Notch pathways in OPMD/OSCC. The limitation of the current study was that all the papers were retrieved from the Scopus database and thus may overlook important research in other databases. Moreover, the more recent important research could not accumulate enough citations at the time of this study. Overall, this study would help in improving in investigations on key signaling pathways in oral carcinogenesis, and provide new insights for researchers to delve into the mechanisms of Wnt and Notch related OPMD/OSCC and translate into clinical studies.

Declaration of competing interest

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

Acknowledgments

This work was supported by National Natural Science Foundation of China (82205200) and Natural Science Foundation of Hunan Province (2024JJ9540).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2025.06.015.

References

1. Hussein NI, Molina AH, Sunga GM, et al. Localized intratumoral delivery of immunomodulators for oral cancer and oral potentially malignant disorders. *Oral Oncol* 2024;158:106986.
2. Purwaningsih NMS, Khor GH, Nik Mohd Rosdy NMM, Abdul Rahman EO. Wnt pathway in oral cancer: a review update. *Saudi Dent J* 2021;33:813—8.
3. Nigam K, Srivastav RK. Notch signaling in oral pre-cancer and oral cancer. *Med Oncol* 2021;38:139.
4. Alamoud KA, Kukuruzinska MA. Emerging insights into Wnt/β-catenin signaling in head and neck cancer. *J Dent Res* 2018;97:665—73.
5. Fukusumi T, Califano JA. The Notch pathway in head and neck squamous cell carcinoma. *J Dent Res* 2018;97:645—53.
6. Liu Q, Deng Y, Liu W, Shen Z. The scientometric characteristics of Lichen planus in stomatology and dermatology journals: a comparative study. *J Dent Sci* 2024;19:1934—41.
7. Zhang Z, Zhu H, Ren Z, Shi H, Liu W. A scientometric and comparative study of Sjogren's syndrome research by rheumatologists and stomatologists. *J Dent Sci* 2024;19:1499—505.
8. Xu W, Li C, Liu Q, Liu W, Wang X. A scientometric study of oral cancer research in South and Southeast Asia with emphasis on risk factors control. *J Dent Sci* 2024;19:2157—62.
9. Liu T, Zhao J, Zhang X, Wang Y, Wang W, Song J. Wnt pathway in bone: knowledge structure and hot spots from 1993 to 2022. *Front Physiol* 2023;14:1279423.
10. Jiang G, Huang CK, Zhang X, et al. Wnt signaling in liver disease: emerging trends from a bibliometric perspective. *PeerJ* 2019;7:e7073.
11. Lei K, Wang X, Liu Y, Sun T, Xie W. Global research hotspots and trends of the Notch signaling pathway in the field of cancer: a bibliometric study. *Am J Transl Res* 2022;14:4918—30.
12. Li Y, Huang L, Hu Q, et al. WNT7B promotes cancer progression via WNT/β-catenin signaling pathway and predicts a poor prognosis in oral squamous cell carcinoma. *BMC Oral Health* 2024;24:1335.
13. Zhao R, Wang S, Tan L, Li H, Liu J, Zhang S. IGFL2-AS1 facilitates tongue squamous cell carcinoma progression via Wnt/β-catenin signaling pathway. *Oral Dis* 2023;29:469—82.
14. Vijayakumar G, Narwal A, Kamboj M, Sen R. Association of SOX2, OCT4 and WNT5A expression in oral epithelial dysplasia and oral squamous cell carcinoma: an immunohistochemical study. *Head Neck Pathol* 2020;14:749—57.
15. Prgomet Z, Andersson T, Lindberg P. Higher expression of WNT5A protein in oral squamous cell carcinoma compared with dysplasia and oral mucosa with a normal appearance. *Eur J Oral Sci* 2017;125:237—46.
16. Khan W, Haragannavar VC, Rao RS, et al. P-Cadherin and WNT5A expression in assessment of lymph node metastasis in oral squamous cell carcinoma. *Clin Oral Investig* 2022;26:259—73.
17. Ogi K, Iwamoto T, Sasaya T, et al. Notch signaling genes and CD8+ T-cell dynamics: their contribution to immune-checkpoint inhibitor therapy in oral squamous cell carcinoma: a retrospective study. *Cancer Med* 2024;13:e6985.
18. Wang J, Yang L, Mei J, et al. Knockdown of Notch suppresses epithelial-mesenchymal transition and induces angiogenesis in oral submucous fibrosis by regulating TGF-β1. *Biochem Genet* 2024;62:1055—69.
19. Sadeghi ES, Nematpour FS, Mohtasham N, Mohajertehran F. The oncogenic role of NOTCH1 as biomarker in oral squamous cell carcinoma and oral Lichen planus. *Dent Res J* 2023;20:102.
20. Pandey A, Bhuvanadas S, Joseph JP, Jayaraj R, Devi A. Notch signalling: a potential therapeutic pathway in oral squamous cell carcinoma. *Endocr, Metab Immune Disord: Drug Targets* 2021;21:2159—68.

21. Patni AP, Harishankar MK, Joseph JP, Sreeshma B, Jayaraj R, Devi A. Comprehending the crosstalk between Notch, Wnt and Hedgehog signaling pathways in oral squamous cell carcinoma - clinical implications. *Cell Oncol* 2021;44:473—94.

22. Chen Y, Chen Y, Liu W. Chaperonin containing TCP1 subunit 6A may activate Notch and Wnt pathways to facilitate the malignant behaviors and cancer stemness in oral squamous cell carcinoma. *Cancer Biol Ther* 2024;25:2287122.