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Research Progress of Transient Receptor Potential Melastatin Family in Head and Neck Squamous Cell Carcinoma

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is the seventh leading cause of mortality among malignant tumors globally. Patients face a poor prognosis and low five-year survival rate due to late-stage diagnosis, high recurrence rate, and metastasis rate. Calcium ion channels are critically involved in tumorigenesis, development, and metastasis, participating in mechanisms such as cell proliferation, apoptosis, invasion, migration, and regulation of the tumor microenvironment. Among these channels, the transient receptor potential melastatin ion channel (TRPM) has been rapidly studied in HNSCC in recent years. Evidence suggests that TRPM channels play both promoting and suppressing roles in the progression of HNSCC, highlighting their potential as diagnostic and prognostic biomarkers, as well as therapeutic targets. This review summarizes the research findings of the TRPM family in the field of HNSCC, providing new insights into prognosis and targeted molecular therapy.

Keywords

TRPM Channels, Head-And-Neck Squamous Cell Carcinoma, Biomarker, Therapeutic Target

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the most common malignant tumor in the head and neck region, representing a major public health challenge worldwide. According to the GLOBOCAN 2020 statistical report, HNSCC accounts for over 830,000 new cases and 430,000 deaths annually worldwide,

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ranking seventh globally in both incidence and mortality rates [1]. Regions in Southeast Asia exhibit a particularly high incidence. In 2022, China recorded over 140,000 new cases, resulting in 80,500 deaths—accounting for 3.1% of all cancer fatalities and ranking seventh among all cancer types [2]. Early symptoms of HNSCC lack specificity, resulting in the majority of patients being diagnosed with locally advanced or metastatic disease. Furthermore, 50% - 60% of HNSCC patients experience recurrence or distant metastasis within two years [3]. Consequently, HNSCC patients face an extremely poor prognosis, with a five-year survival rate below 50%. Surgery, radiotherapy, and platinum-based chemotherapy often carry severe side effects such as dysphagia and organ dysfunction, significantly impairing patients' quality of life [4]. The advent of targeted therapies and immune checkpoint inhibitors has expanded treatment options for HNSCC, achieving durable responses in some patients. However, these therapies demonstrate limited efficacy in recurrent or metastatic cases [5]. Consequently, identifying safer and more effective therapeutic targets, along with biomarkers for accurate response prediction, holds significant importance.

Calcium ion channels participate in the pathological processes of various diseases, and their abnormal expression and dysfunction are closely associated with tumors. Consequently, targeting these channels with calcium channel blockers has emerged as a promising therapeutic strategy for cancer management. Current pharmacological development in this area primarily focuses on two major classes: transient receptor potential (TRP) channels and voltage-gated calcium channels (VGCC/Cavs) [6]. TRP channels belong to the cellular membrane calcium transport system, which are expressed in normal epithelial cells. They promote uncontrolled proliferation, abnormal differentiation, and impaired apoptosis, leading to uncontrolled cancer spread and tumor invasion [7]. Experimental studies have confirmed the oncogenic role of TRP channels in various cancers, including melanoma, glioblastoma, prostate cancer, and breast adenocarcinoma [8]. Among TRP channel subfamilies, Transient Receptor Potential Melastatin (TRPM) channels constitute the largest group. They act as crucial cellular sensors and signal transducers, finely regulating intracellular and extracellular ion homeostasis [9]. Recent studies have demonstrated the immense potential of the TRPM family in HNSCC diagnosis, prognosis, and therapeutic approaches. This article briefly outlines the composition and physiological functions of TRPM family members, systematically elucidates their mechanisms of action and latest findings in HNSCC development, and explores current clinical applications and challenges associated with TRPM.

2. TRPM Family

The TRPM family comprises non-selective calcium channels, consisting of TRPM1 through TRPM8. Each member contains three domains: an N-terminal region, a transmembrane TRPM domain (TMD), and a C-terminal region. The N-terminal domain contains four Melastatin Homology Regions (MHRs) that sense external

stimuli. The transmembrane region S4 serves as the voltage-sensing domain, while the P-loop between S5 and S6 forms the ion channel pore [10]. All TRPM proteins function as cation channels. Most are calcium-permeable (except TRPM4/5), enabling them to influence diverse signaling pathways by modulating cytosolic calcium levels. The C-terminal domains of different members exhibit significant structural variation, but all contain highly conserved TRP box sequences and coiled-coil domains, the latter playing a crucial role in polymer complex formation [11]. Different members participate in distinct physiological and pathological processes. TRPM1 channels are critical for normal melanocyte pigmentation, are expressed in melanocytes and the retina, and are associated with melanoma. TRPM2 senses oxidative stress and is closely linked to diabetes and inflammatory neurodegenerative diseases. TRPM3 participates in pain and temperature perception. TRPM4 and TRPM5 are involved in taste transduction. TRPM6 and TRPM7 regulate magnesium homeostasis. TRPM7 features a unique α-kinase domain at its C-terminus, which phosphorylates the myosin IIA heavy chain to regulate cytoskeleton and focal adhesion dynamics, thereby driving cell migration. In TRPM8, the S5-S6 pore region serves as the binding site for menthol, while the C-terminal domain is involved in temperature sensing and interactions with signaling molecules such as PIP_2. TRPM8 detects cold sensation, responds to menthol stimulation, and serves as a key target in prostate cancer [12]. Additionally, TRPM channels influence tumor progression through microenvironment sensing, signaling pathway interactions, and autophagy regulation [13].

3. The Role and Mechanism of TRPM in HNSCC

While the roles of TRPM3 and TRPM5 remain less explored, the remaining members exhibit differential expression in HNSCC. For instance, TRPM1 mRNA levels are significantly downregulated in HNSCC tissues [14]. Research indicates that upregulation of miR-211 within the sixth intron of the TRPM1 gene and downregulation of TGFβRII are closely associated with poor prognosis in HNSCC. Functionally, miR-211 promotes HNSCC progression by directly targeting TGFβRII through the miR-211-TGFβRII-c-Myc axis [15]. As a potential therapeutic target, TRPM1 downregulation may be implicated in HNSCC tumorigenesis or progression, though specific mechanisms require further validation. Radiotherapy for head and neck cancer frequently causes irreversible salivary gland damage, severely compromising patients' quality of life. Radiation mediates irreversible salivary gland injury via the PARP1-ADPR-TRPM2 pathway. Targeting this pathway (via gene knockout, 3-AB, or TPL) significantly restores secretory function, offering a potential therapeutic strategy for head and neck cancer radiotherapy patients [16]. TRPM4, recently identified as a key player in necrosis induced by sodium overload (NECSO), is highly expressed in HNSCC tumor tissues [17]. ROC curve analysis demonstrated moderate diagnostic value of TRPM4 for HNSCC. Co-localization of TRPM4 with integrin $\alpha2\beta1$ (ITGA2) synergistically aids HNSCC cells in resisting cell death induced by osmotic rupture and sodium-dependent cell death

[18]. TRPM7 is overexpressed in nasopharyngeal carcinoma, laryngeal carcinoma, and hypopharyngeal carcinoma. Qiao *et al.* demonstrated that salivary magnesium activates the AKT/mTOR pathway via TRPM7 channels to promote HNSCC progression, while TRPM7 inhibitors (e.g., FTY720) block magnesium's oncogenic effects [19]. Additional studies revealed that TRPM7 promotes metastasis, stem cell properties, and cisplatin resistance in HNSCC through the calcineurin/NFAT pathway. Silencing TRPM7 significantly suppressed these malignant phenotypes and enhanced chemotherapy efficacy *in vitro* and *in vivo* [20]. This supports TRPM7 as a novel therapeutic target, with its inhibitors potentially improving HNSCC patient prognosis. The research highlights the potential of ion channels in cancer treatment. A study analyzed that patients with high TRPM8 expression exhibited significantly reduced survival rates, positively correlated with histological grade and lymph node metastasis. Cancer tissues from drinkers or smokers exhibited significantly higher TRPM8 expression than adjacent noncancerous tissues. *In vitro* experiments showed that betel nut alkaloid treatment of betel-chewed OSCC cells (SAS, OECM-1) significantly increased TRPM8 mRNA and protein expression [21]. This indicates TRPM8 plays a key role in HNSCC malignant progression and metastasis. Risk factors such as alcohol, tobacco, and arecoline may promote HNSCC development by upregulating TRPM8 expression. However, the molecular mechanisms of TRPM8 in HNSCC remain unclear. Owing to the anatomical and physiological complexity of the head and neck region, HNSCC exhibits considerable heterogeneity depending on the site of origin. The roles of TRPM channels across different HNSCC subsites and their underlying mechanisms are summarized in **Table 1**.

3.1. Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) exhibits a high global incidence rate, with approximately 350,000 new cases diagnosed annually. Alcohol consumption, tobacco use, betel nut chewing, and HPV infection are recognized as high-risk factors [22]. Among these, tongue squamous cell carcinoma (TSCC) represents the most prevalent form of oral squamous cell carcinoma. TRPM2, TRPM6, TRPM7, and TRPM8 all exhibit overexpression in OSCC. Zhao *et al.* observed significantly elevated TRPM2 mRNA and protein levels in human tongue squamous cell carcinoma samples. In SCC9 cells and tongue cancer tissues, TRPM2 primarily localizes to the nucleus, whereas normal tissues show no nuclear localization. This suggests TRPM2's function in OSCC may be related to its membrane or nuclear localization. Elevated early-stage membrane TRPM2 levels mediate oxidative stress-induced Ca^{2+} influx, activating the caspase pathway and inhibiting early tumor growth. In later stages, membrane depletion and nuclear enrichment of TRPM2 maintain genomic stability, playing a crucial role in OSCC survival and migration. TRPM2 knockout exhibits tumor-suppressing effects by inhibiting tumor cell migration and promoting apoptosis [23]. Unfortunately, the specific triggers for the enrichment of TRPM2 in cancer cells remain unknown.

Table 1. Basic characteristics of the included literature (n = 17).

Cancer Type	TRPMs	Methods/Signaling pathway	Function/Result	Reference
HNSCC	TRPM1		mRNA downregulation	[14]
	TRPM2	PARP1-ADPR-TRPM2	radiation-induced salivary gland damage	[16]
	TRPM4		overexpression	[18]
		Colocalization Synergy of ITGA2	protect cancer cells from NECSO	
	TRPM7	AKT/mTOR	promote HNSCC progression	[19]
		calcineurin/NFAT	Proliferation, migration, cisplatin resistance	[20]
	TRPM8		overexpression	[21]
OSCC	TRPM2		Protein and mRNA upregulation	[23]
		oxidative stress、caspase pathway	early cancer suppression, mid-to-late-stage proliferation, and migration	
	TRPM6		overpexpression	[25]
	TRPM7	PL	cancer suppression	[27]
	TRPM8	Menthol	migration, invasion	[26]
NPC	TRPM7		overexpression	[30]
		CICR	migration, invasion	[29]
		JAK2/STAT3	proliferation	[31]
HPSCC	TRPM7	Midazolam	cancer suppression	[33]
NPC	TRPM2	GAL	enhance cisplatin sensitivity	[37]
		DOX	cancer suppression	[38]
	TRPM7	hsa_circ_0023305/miR-218-5p/TRPM7	proliferation, migration, invasion	[36]

Subsequently, Zhu *et al.* found TRPM2 expression levels significantly correlated with histological grading: mRNA and protein expression were markedly upregulated in well-differentiated TSCC, while the opposite trend was observed in moderately or poorly differentiated tissues. Poorly differentiated tissues exhibit higher oxidative stress levels [24]. Additionally, TRPM6 was found to regulate calcium signaling and promote oral carcinogenesis, with its expression positively correlated with lesion severity, metastasis, and staging [25]. Unlike TRPM2, which relies on oxidative stress regulation for carcinogenesis, the mechanism underlying TRPM6 remains unclear and warrants future investigation. TRPM8 is implicated in cold perception and menthol-induced cold sensation. A Japanese study revealed that menthol enhances OSCC cell migration and invasion by increasing MMP-9 activity, while the TRPM8 antagonist RQ inhibits this invasion by blocking both menthol-induced and intrinsic TRPM8 activity [26]. Another study in the same year demonstrated that the anticancer drug piperlongumine (PL) powerfully inhibits TRPM7, exerting its OSCC-suppressing effect by downregulating TRPM7 expression and antagonizing channel currents [27]. These studies reveal

the therapeutic potential of TRPM channels as targets, laying a theoretical foundation for developing TRPM channel antagonists (such as RQ) for clinical intervention.

3.2. Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a malignant tumor exhibiting significant geographic and ethnic disparities, with high incidence rates in Southeast Asia, Alaska, and Greenland. It is closely associated with long-term smoking, alcohol consumption, and Epstein-Barr virus infection [28]. The concealed location of NPC and its atypical early symptoms make diagnosis challenging, leading to significantly reduced 5-year survival rates. While NPC is generally sensitive to chemoradiotherapy, recent therapeutic advances have increasingly integrated immunotherapy with radiation, showing promising progress. Current research on NPC and TRPM channels primarily focuses on TRPM7. Chen *et al.* demonstrated that TRPM7 promotes NPC cell migration and metastasis by regulating calcium-induced calcium release (CICR) through Ca^{2+} influx [29]. The same team further reported that high TRPM7 expression correlates positively with clinical stage, lymph node metastasis, and distant metastasis [30]. High TRPM7 expression serves as an independent adverse prognostic factor for 5-year overall survival. They validated the molecular mechanisms by which TRPM7 promotes NPC metastasis: calcium signaling regulation, cytoskeletal remodeling, and modulation of the metastatic microenvironment. Qin *et al.* found that knocking out TRPM7 reduced STAT3 phosphorylation (pSTAT3) levels, downregulated anti-apoptotic factors, increased SOCS3 (STAT3 inhibitor) expression, and enhanced sensitivity to radiotherapy [31]. This revealed that TRPM7 regulates tumor proliferation by continuously activating the JAK2/STAT3 signaling pathway. TRPM7 expression levels predict radiosensitivity, and its knockout significantly enhances radiotherapy efficacy. Targeting the TRPM7-STAT3 axis may emerge as a novel therapeutic approach for NPC combined with radiotherapy.

3.3. Hypopharyngeal Squamous Cell Carcinoma and Laryngeal Squamous Cell Carcinoma

Hypopharyngeal squamous cell carcinoma (HPSCC) originates in regions such as the pyriform sinus, retropharyngeal space, and posterior pharyngeal wall. Due to the absence of specific symptoms during early stages, the disease is frequently diagnosed at an advanced phase, often accompanied by a high incidence of cervical lymph node metastasis and a correspondingly poor prognosis [32]. TRPM7 exhibits high expression in nasopharyngeal carcinoma, hypopharyngeal carcinoma, and laryngeal carcinoma. Dou *et al.* found that midazolam inhibits TRPM7 mRNA expression, leading to G_0/G_1 phase cell cycle arrest in HPSCC cells (e.g., the FaDu line) and preventing entry into the S-phase, thereby suppressing proliferation. The specific TRPM7 agonist bradykinin reverses midazolam's proliferation-inhibitory effect [33]. Other researchers suggest midazolam may also inhibit cancer cell

growth through multiple pathways, including inducing endoplasmic reticulum stress (ER stress), inhibiting the Akt signaling pathway, and regulating cyclin proteins such as p21 and p27. The specific mechanisms may vary depending on the cancer cell type [34].

Early-stage laryngeal squamous cell carcinoma (LSCC) may present with symptoms such as hoarseness, throat discomfort or pain, coughing, or sputum production. Patients diagnosed early and treated surgically generally have favorable outcomes, whereas advanced-stage patients experience severely impaired quality of life due to voice dysfunction [35]. Research has identified significantly elevated expression of hsa_circ_0023305 in 30 LSCC tissue samples [36]. High expression of hsa_circ_0023305 correlates positively with LSCC stage, lymph node metastasis, and poor prognosis. Acting as a molecular sponge, hsa_circ_0023305 sequesters miR-218-5p, thereby releasing its inhibitory effect on TRPM7 and upregulating TRPM7 expression. This process drives LSCC proliferation, invasion, and migration. This reveals a novel target axis—hsa_circ_0023305/miR-218-5p/TRPM7—offering potential molecular targets for early LSCC diagnosis and targeted therapy. Recent studies indicate TRPM2 is also a critical LSCC target. Yazgan *et al.* demonstrated that gallic acid (GAL) enhances cisplatin-induced oxidative stress by activating TRPM2 channels, thereby promoting death in LSCC cells (Hep-2) [37]. This suggests GAL holds promise as an effective sensitizer for cisplatin therapy in laryngeal cancer. Another research team observed that doxorubicin (DOX) significantly enhances TRPM2 channel activation and ROS production in Hep-2 cells, thereby initiating apoptotic pathways leading to cell death [38]. However, combination therapy with the TRPM2 antagonist ACA mitigated DOX-induced oxidative stress and inflammatory responses. Currently, both conclusions are based on cellular experiments and require further validation through animal models and clinical trials.

Currently, most studies have not integrated the expression and function of the TRPM family with the different subtypes of HNSCC. Different HNSCC subtypes exhibit distinct core signaling pathway profiles, while changes in TRPM expression are cancer-specific.

4. Summary and Outlook

In summary, the TRPM family participates in the development and progression of HNSCC through multiple mechanisms. TRPM channels show considerable promise as tools for prognostic assessment and as potential therapeutic targets in HNSCC. In prognosis, researchers have established TFBS (TRPC1/3/6 + TRPV2/4 + TRPM8) as an independent prognostic biomarker for HNSCC, reflecting tumor immune status and key oncogenic pathways, though further external validation is warranted [39]. For therapeutic targets, the TRPM8 modulator D3263 has entered Phase I clinical trials for the treatment of prostate cancer [40]. However, most TRPM targets in HNSCC remain confined to *in vitro* experiments, and translating basic research into clinical applications faces significant challenges.

A primary obstacle is therapeutic specificity, TRPMs are widely distributed throughout the human body, and inhibition may induce toxic side effects, compromising drug efficacy and accuracy. Developing targeted delivery is crucial to addressing this issue. Approaches include exploring antibody-drug conjugates (ADCs), prodrug systems, or nanocarriers, as well as leveraging the tumor microenvironment or tumor-specific antigens for targeted delivery. Furthermore, the functional complexity of TRPM channels presents another layer of difficulty. The same TRPM member may perform opposing roles across different cancers or even at distinct stages of the same cancer. For instance, TRPM2 acts as a tumor suppressor in early-stage oral squamous cell carcinoma but may promote tumor progression in advanced stages. Finally, HNSCC exhibits diverse signaling pathways, and single-targeted TRPM channel inhibition may trigger compensatory mechanisms. Consequently, combination therapies that integrate TRPM modulation with conventional modalities like radiotherapy, chemotherapy, molecularly targeted agents, or immune checkpoint inhibitors hold synergistic potential to overcome this adaptability and improve outcomes. Despite these challenges, advancing research into the biological functions of the TRPM family and technological advancements hold promise for targeted TRPM channel therapies to deliver novel breakthroughs in cancer treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Han, B., Zheng, R., Zeng, H., Wang, S., Sun, K., Chen, R., *et al.* (2024) Cancer Incidence and Mortality in China, 2022. *Journal of the National Cancer Center*, **4**, 47-53. https://doi.org/10.1016/j.jncc.2024.01.006

[3] Mody, M.D., Rocco, J.W., Yom, S.S., Haddad, R.I. and Saba, N.F. (2021) Head and Neck Cancer. *The Lancet*, **398**, 2289-2299. https://doi.org/10.1016/s0140-6736(21)01550-6

[4] Darvin, P., Toor, S.M., Sasidharan Nair, V. and Elkord, E. (2018) Immune Checkpoint Inhibitors: Recent Progress and Potential Biomarkers. *Experimental & Molecular Medicine*, **50**, 1-11. https://doi.org/10.1038/s12276-018-0191-1

[5] Shaikh, H., Karivedu, V. and Wise-Draper, T.M. (2021) Managing Recurrent Metastatic Head and Neck Cancer. *Hematology/Oncology Clinics of North America*, **35**, 1009-1020. https://doi.org/10.1016/j.hoc.2021.05.009

[6] Bidaud, I., Mezghrani, A., Swayne, L.A., Monteil, A. and Lory, P. (2006) Voltage-gated Calcium Channels in Genetic Diseases. *Biochimica et Biophysica Acta—Molecular Cell Research*, **1763**, 1169-1174. https://doi.org/10.1016/j.bbamcr.2006.08.049

[7] Santoni, G. and Farfariello, V. (2011) TRP Channels and Cancer: New Targets for Diagnosis and Chemotherapy. *Endocrine*, *Metabolic & Immune Disorders—Drug Targets*, **11**, 54-67. https://doi.org/10.2174/187153011794982068

[8] Liu, Z., Wu, H., Wei, Z., Wang, X., Shen, P., Wang, S., *et al.* (2016) TRPM8: A Potential Target for Cancer Treatment. *Journal of Cancer Research and Clinical Oncology*, **142**, 1871-1881. https://doi.org/10.1007/s00432-015-2112-1

[9] Hantute-Ghesquier, A., Haustrate, A., Prevarskaya, N. and Lehen'kyi, V. (2018) TRPM Family Channels in Cancer. *Pharmaceuticals*, **11**, Article 58. https://doi.org/10.3390/ph11020058

[10] Held, K., Gruss, F., Aloi, V.D., Janssens, A., Ulens, C., Voets, T., *et al.* (2018) Mutations in the Voltage-Sensing Domain Affect the Alternative Ion Permeation Pathway in the TRPM3 Channel. *The Journal of Physiology*, **596**, 2413-2432. https://doi.org/10.1113/jp274124

[11] Jiang, L.H. (2007) Subunit Interaction in Channel Assembly and Functional Regulation of Transient Receptor Potential Melastatin (TRPM) Channels. *Biochemical Society Transactions*, **35**, 86-88. https://doi.org/10.1042/bst0350086

[12] Liu, Q., Hu, M., Li, S., Zhang, X., Zhang, R., Lyu, H., *et al.* (2024) TRPM Channels in Human Cancers: Regulatory Mechanism and Therapeutic Prospects. *Biomarker Research*, **12**, Article No. 152. https://doi.org/10.1186/s40364-024-00699-2

[13] Ciaglia, T., Vestuto, V., Bertamino, A., González-Muñiz, R. and Gómez-Monterrey, I. (2023) On the Modulation of TRPM Channels: Current Perspectives and Anticancer Therapeutic Implications. *Frontiers in Oncology*, **12**, Article 1065935. https://doi.org/10.3389/fonc.2022.1065935

[14] Qin, F., Lao, L., Huang, M., Tan, H., Jin, X., Ma, X., *et al.* (2020) Evaluation of the TRPM Protein Family as Potential Biomarkers for Various Types of Human Cancer Using Public Database Analyses. *Experimental and Therapeutic Medicine*, **20**, 770-785. https://doi.org/10.3892/etm.2020.8739

[15] Chu, T.H., Yang, C.C., Liu, C.J., Lui, M.T., Lin, S.C. and Chang, K.W. (2013) miR-211 Promotes the Progression of Head and Neck Carcinomas by Targeting TGFβRII. *Cancer Letters*, **337**, 115-124. https://doi.org/10.1016/j.canlet.2013.05.032

[16] Hossain, M.Z., Ando, H., Unno, S., Masuda, Y. and Kitagawa, J. (2018) Activation of TRPV1 and TRPM8 Channels in the Larynx and Associated Laryngopharyngeal Regions Facilitates the Swallowing Reflex. *International Journal of Molecular Sciences*, **19**, Article 4113. https://doi.org/10.3390/ijms19124113

[17] Fu, W., Wang, J., Li, T., Qiao, Y., Zhang, Z., Zhang, X., *et al.* (2025) Persistent Activation of TRPM4 Triggers Necrotic Cell Death Characterized by Sodium Overload. *Nature Chemical Biology*, **21**, 1238-1249. https://doi.org/10.1038/s41589-025-01841-3

[18] Dai, Y., Wang, H., Wang, W. and Zhuang, X. (2025) Multidimensional Pan Cancer Analysis of the Sodium Induced Cell Death Gene TRPM4. *Scientific Reports*, **15**, Article No. 29768. https://doi.org/10.1038/s41598-025-15082-w

[19] Qiao, W., Lan, X.M., Ma, H.X., Chan, J.Y.K., Lui, V.W.Y., Yeung, K.W.K., *et al.* (2019) Effects of Salivary Mg on Head and Neck Carcinoma via TRPM7. *Journal of Dental Research*, **98**, 304-312. https://doi.org/10.1177/0022034518813359

[20] Chen, T.M., Huang, C.M., Hsieh, M.S., Lin, C.S., Lee, W.H., Yeh, C.T. and Liu, S.C. (2022) TRPM7 via Calcineurin/NFAT Pathway Mediates Metastasis and Chemotherapeutic Resistance in Head and Neck Squamous Cell Carcinoma. *Aging*, **14**, 5250-5270. https://doi.org/10.18632/aging.204154

[21] Lin, N.C., Vu Nguyen, T.H., Shih, Y.H., Chen, Y.H., Shen, Y.W., *et al.* (2024) Association of Higher Transient Receptor Potential Melastatin 8 Expression with Higher Tumor Histologic Grades, Lymph Node Metastasis, Risk Factors, and Worse Survival in Patients with Head and Neck Squamous Cell Carcinoma. *Journal of Dental Sci-*

ences, **19**, 492-501. https://doi.org/10.1016/j.jds.2023.09.007

[22] Tan, Y., Wang, Z., Xu, M., Li, B., Huang, Z., Qin, S., *et al.* (2023) Oral Squamous Cell Carcinomas: State of the Field and Emerging Directions. *International Journal of Oral Science*, **15**, Article No. 44. https://doi.org/10.1038/s41368-023-00249-w

[23] Zhao, L.Y., Xu, W.L., Xu, Z.Q., Qi, C., Li, Y., *et al.* (2016) The Overexpressed Functional Transient Receptor Potential Channel TRPM2 in Oral Squamous Cell Carcinoma. *Scientific Reports*, **6**, Article No. 3841. https://doi.org/10.1038/srep38471

[24] Zhu, F., Cai, X., Yang, X., He, J., Wang, C., Wang, M., *et al.* (2020) TRPM2 Expression Levels Are Associated with Histological Grading in Patients with Tongue Squamous Cell Carcinoma. *Molecular Medicine Reports*, **22**, 3566-3574. https://doi.org/10.3892/mmr.2020.11417

[25] Wang, Y.Y., Wang, W.C., Su, C.W., Hsu, C.W., Yuan, S.S. and Chen, Y.K. (2023) Overexpression of Transient Receptor Potential Melastatin 6 during Human Oral Squamous Cell Carcinogenesis. *Journal of Dental Sciences*, **18**, 382-391. https://doi.org/10.1016/j.jds.2022.11.002

[26] Okamoto, Y., Ohkubo, T., Ikebe, T. and Yamazaki, J. (2012) Blockade of TRPM8 Activity Reduces the Invasion Potential of Oral Squamous Carcinoma Cell Lines. *International Journal of Oncology*, **40**, 1431-1440.

[27] Su, T., Chen, Y.H., Wu, K.K. and Xu, X.H. (2024) Anti-Cancer Agent Piperlongumine Is an Inhibitor of Transient Receptor Potential Melastatin 7 Channel in Oral Squamous Cell Carcinoma. *Journal of Oral Biosciences*, **66**, 430-438. https://doi.org/10.1016/j.job.2024.03.002

[28] Chang, E.T. and Adami, H.O. (2006) The Enigmatic Epidemiology of Nasopharyngeal Carcinoma. *Cancer Epidemiology, Biomarkers & Prevention*, **15**, 1765-1777. https://doi.org/10.1158/1055-9965.epi-06-0353

[29] Chen, J.P., Luan, Y., You, C.X., Chen, X.H., Luo, R.C. and Li, R. (2010) TRPM7 Regulates the Migration of Human Nasopharyngeal Carcinoma Cell by Mediating Ca^{2+} Influx. *Cell Calcium*, **47**, 425-432. https://doi.org/10.1016/j.ceca.2010.03.003

[30] Chen, J.P., Wang, J., Luan, Y., Wang, C.X., Li, W.H., Zhang, J.B., *et al.* (2015) TRPM7 Promotes the Metastatic Process in Human Nasopharyngeal Carcinoma. *Cancer Letters*, **356**, 483-490. https://doi.org/10.1016/j.canlet.2014.09.032

[31] Qin, Y., Liao, Z.W., Luo, J.Y., Wu, W.Z., Lu, A.S., *et al.* (2016) Functional Characterization of TRPM7 in Nasopharyngeal Carcinoma and Its Knockdown Effects on Tumorigenesis. *Tumor Biology*, **37**, 9273-9283. https://doi.org/10.1007/s13277-015-4636-z

[32] Bozec, A., Poissonnet, G., Dassonville, O. and Culié, D. (2023) Current Therapeutic Strategies for Patients with Hypopharyngeal Carcinoma: Oncologic and Functional Outcomes. *Journal of Clinical Medicine*, **12**, Article 1237. https://doi.org/10.3390/jcm12031237

[33] Dou, Y., Li, Y., Chen, J., Wu, S., Xiao, X., Xie, S., *et al.* (2013) Inhibition of Cancer Cell Proliferation by Midazolam by Targeting Transient Receptor Potential Melastatin 7. *Oncology Letters*, **5**, 1010-1016. https://doi.org/10.3892/ol.2013.1129

[34] Jiao, J., Wang, Y., Sun, X. and Jiang, X. (2017) Insights into the Roles of Midazolam in Cancer Therapy. *Evidence-Based Complementary and Alternative Medicine*, **2017**, Article 3826506. https://doi.org/10.1155/2017/3826506

[35] Liberale, C., Soloperto, D., Marchioni, A., Monzani, D. and Sacchetto, L. (2023) Updates on Larynx Cancer: Risk Factors and Oncogenesis. *International Journal of Molecular Sciences*, **24**, Article 12913. https://doi.org/10.3390/ijms241612913

[36] Zhang, Y., Tian, K., Zhou, E., Xue, X., Yan, S., Chen, Y., *et al.* (2021) Hsa_circ_0023305 Enhances Laryngeal Squamous Cell Carcinoma Progression and Modulates TRPM7 via miR-218-5p Sponging. *BioMed Research International*, **2021**, Article 9968499. https://doi.org/10.1155/2021/9968499

[37] Yazgan, Y. and Cinar, R. (2025) Gallic Acid Enhances Cisplatin-Induced Death of Human Laryngeal Cancer Cells by Activating the TRPM2 Channel. *Doklady Biochemistry and Biophysics*, **521**, 221-231. https://doi.org/10.1134/s1607672924601276

[38] Yağcı, T., Çınar, R., Altıner, H.İ., Dündar, R. and Yıldızhan, K. (2025) The Role of TRPM2 Channel in Doxorubicin-Induced Cell Damage in Laryngeal Squamous Cancer Cells. *Doklady Biochemistry and Biophysics*, **520**, 123-129. https://doi.org/10.1134/s1607672924601070

[39] Pan, F., Wang, K., Zheng, M., Ren, Y., Hao, W. and Yan, J. (2022) A TRP Family Based Signature for Prognosis Prediction in Head and Neck Squamous Cell Carcinoma. *Journal of Oncology*, **2022**, 1-13. https://doi.org/10.1155/2022/8757656

[40] Izquierdo, C., Martín-Martínez, M., Gómez-Monterrey, I. and González-Muñiz, R. (2021) TRPM8 Channels: Advances in Structural Studies and Pharmacological Modulation. *International Journal of Molecular Sciences*, **22**, Article 8502. https://doi.org/10.3390/ijms22168502