International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 14, No. 1, 2026

RAB7A in Oral Squamous Cell Carcinoma: A Key Regulator of Autophagy-Lysosome Dynamics and Cellular Signaling

Yubin Pang, Linxuan Zhang, Yingjiu Wang, Yuwei Jia, Xintong Han, Wei Dong, Junyuan Zhang *

North China University of Science and Technology, Tangshan, Hebei, 063210, China

*** Corresponding author:** Junyuan Zhang

Abstract: Oral squamous cell carcinoma (OSCC) is the most common malignancy of the head and neck region. Despite advances in treatment, its prognosis has remained poor over the years, largely due to its high invasiveness and resistance to therapy. A deeper understanding of the molecular mechanisms underlying OSCC initiation and progression is essential for the development of novel diagnostic and therapeutic strategies. This review summarizes the role of Ras-related protein Rab-7a (RAB7A) in various tumors and explores its potential functions in OSCC. We also discuss RAB7A-related research in oral diseases such as periodontitis and highlight its key role in regulating autophagic homeostasis and inflammatory responses via post-translational modifications. Furthermore, given the abnormal activation of signaling pathways such as Hippo/Yes-associated protein (Hippo/YAP), phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR), and mitogen-activated protein kinase (MAPK) in OSCC, we infer the possibility that RAB7A may contribute to OSCC progression by mediating intracellular transport and integrating signals from these pathways. Overall, RAB7A serves as a pivotal hub molecule linking the autophagy-lysosome system to oncogenic signaling pathways. In-depth investigation of its role in OSCC is expected to provide precise target sites for targeted drug development, offer new insights into clinical combination therapy, and clarify the core function of RAB7A in the molecular regulatory network of OSCC, thereby establishing a direct association between autophagy regulatory pathways and OSCC progression.

Keywords: RAB7A; Oral Squamous Cell Carcinoma; Signaling Pathway; Autophagy-lysosome.

1. Introduction

Ras-related protein Rab-7a (RAB7A) is a core member of the Rab GTPase family. Its encoding gene is located on human chromosome 3q21.3 [1]. RAB7A is ubiquitously and evolutionarily conserved in eukaryotes. The encoded protein functions as a critical molecular switch controlling endolysosomal system dynamics [2]. As a small GTPase, RAB7A undergoes reversible switching between GTP-bound and GDP-bound states. This conformational transition regulates late endosome maturation, cargo sorting, and lysosomal fusion [3]. It also mediates signal transduction and protein–protein interactions [4].

Oral squamous cell carcinoma (OSCC) is the most prevalent malignancy of the oral and maxillofacial region. It constitutes approximately 90% of all oral malignancies [5]. Late-stage diagnosis, recurrence, metastasis, and the limitations of conventional chemoradiotherapy remain major obstacles to improving patient outcomes [6]. OSCC pathogenesis is closely associated with tobacco use, alcohol consumption, betel quid chewing, and human papillomavirus (HPV) infection. HPV-negative cases predominate and present an urgent need for prognostic improvement [7,8]. Recent advances in spatial transcriptomics and single-cell sequencing have enabled detailed investigation of tumor microenvironment (TME) heterogeneity and molecular regulatory mechanisms in OSCC. The tumor core (TC) and leading edge (LE) exhibit distinct transcriptomic signatures. The LE is enriched in pro-invasive and pro-metastatic genes. This gene signature is conserved across multiple cancer types and correlates with poor prognosis. In contrast, the TC is characterized by elevated expression of genes involved in cell differentiation and is associated with relatively favorable prognosis [9]. The immunosuppressive network within the TME is primarily composed of regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and cancer-associated fibroblasts (CAFs) [10]. These components collectively exert synergistic inhibitory effects through metabolic reprogramming, cytokine secretion, and intercellular communication [11]. Fusobacterium nucleatum, a component of the oral microbiota, promotes TAM polarization via activation of specific signaling pathways, thereby exacerbating tumor invasion [7]. In the therapeutic domain, strategies targeting metabolic pathways, key signaling cascades, and microbial factors have entered clinical investigation. Dual-targeting regimens and combination immunotherapies have demonstrated synergistic potential [12,13]. Nonetheless, challenges persist in OSCC research. These include insufficient selectivity of metabolic inhibitors, heterogeneous treatment responses arising from tumor heterogeneity [14], metabolic resistance in Tregs [15], and the management of immune-related adverse events.

Recent studies have increasingly focused on aberrant activation of canonical oncogenic signaling pathways in OSCC, including phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR), Hippo/Yes-associated protein (Hippo/YAP), and mitogen-activated protein kinase (MAPK) cascades [16]. Meanwhile, RAB7A, a core small GTPase governing late endosomal and lysosomal trafficking, has been implicated in invasion, metastasis, therapeutic resistance, and poor prognosis across multiple solid tumor types. It is now recognized as a pivotal hub linking cellular metabolic adaptation to malignant progression [17]. This review focuses on the biological

functions of RAB7A. It summarizes the role of RAB7A in the progression of various malignancies. Particular emphasis is placed on established signaling pathway aberrations in OSCC. The goal is to explore potential molecular mechanisms through which RAB7A may contribute to OSCC progression. In addition, this review consolidates current knowledge regarding RAB7A in oral diseases and outlines future research directions.

2. The Role of RAB7A in Tumor Progression

RAB7A is a key member of the small GTPases of the Ras superfamily, and its molecular structure and functional regulation are highly conserved and specific. In terms of molecular structure, RAB7A takes a conserved GTP-binding domain as the core functional region, including G1-G5 motifs and Switch I/II switch regions. Among them, the G1-G5 motifs are responsible for the specific binding and hydrolysis of GDP/GTP, and the Switch I/II regions respond to the nucleotide binding state through conformational changes to mediate interactions with downstream effector molecules [18]. In terms of cellular localization, RAB7A is mainly enriched in the membranes of late endosomes and lysosomes, and can dynamically shuttle between the cytoplasm and membrane structures [19]. This localization characteristic makes it a core node connecting intracellular material transport and organelle function regulation, providing a structural basis for its participation in multi-pathway signal transduction. RAB7A is aberrantly expressed in various malignancies and exerts dual regulatory roles. It facilitates tumor proliferation, invasion, metastasis, and chemotherapy resistance by modulating endosomal trafficking, autophagic flux, and signaling pathways. Conversely, it exhibits tumor-suppressive functions in specific tumor contexts. Its expression level is closely associated with clinical prognosis, highlighting its potential as a promising diagnostic marker and therapeutic target.

2.1. Pro-tumorigenic Effects and Regulatory Pathways of RAB7A

In various solid tumors, including pancreatic cancer and hepatocellular carcinoma (HCC), RAB7A typically acts as a key driver of malignant transformation. Its abnormal upregulation is closely linked to tumor progression and poor clinical outcomes.

In pancreatic cancer, multi-omics data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) show that RAB7A is significantly overexpressed in tumor tissues. Cox regression analysis further identifies it as an independent risk factor for poor prognosis in pancreatic adenocarcinoma. This predictive value remains consistent across different clinical subgroups, highlighting its critical role in tumor progression [20]. In HCC, RAB7A directly modulates the YAP1 signaling pathway. It does so by interfering with the binding between YAP1 and 14-3-3, thereby promoting YAP1 nuclear translocation and enhancing its transcriptional activity. This mechanism drives cancer cell proliferation, invasion, and malignant progression [21].

RAB7A also contributes substantially to treatment resistance. In nasopharyngeal carcinoma (NPC), it interacts directly with the anti-apoptotic protein HS1-associated protein X-1z (HAX-1). HAX-1 suppresses RAB7A-mediated autophagosome-lysosome fusion, disrupting autophagic flux and leading to cisplatin resistance [22]. In lung cancer and gastric cancer, elevated RAB7A expression correlates with advanced tumor stage, increased invasiveness, and shorter survival. It also affects chemosensitivity by regulating autophagy-lysosome function, which influences the metabolism and efficacy of chemotherapeutic drugs [23]. In triple-negative breast cancer (TNBC), transcriptomic analysis reveals that RAB7A knockdown alters gene networks involved in cell cycle control, metabolism, and migration. This suggests that RAB7A contributes to tumor phenotype regulation through broad network interactions rather than isolated pathway effects [24].

2.2. Anti-tumorigenic Effects and Regulatory Pathways of RAB7A

In certain tumor contexts, RAB7A can exert anti-tumor effects by cooperating with specific molecular partners. For example, germline mutations in the tumor suppressor gene folliculin (FLCN) are known to predispose individuals to tumors such as fibrofolliculoma and renal cell carcinoma. RAB7A plays a key role in mediating the tumor suppressive function of FLCN. Specifically, FLCN promotes the endosomal transport of epidermal growth factor receptor (EGFR) and negatively regulates its signaling pathway through the activation of RAB7A [25].

In melanoma, the tumor suppressive role of RAB7A is closely linked to the microRNA regulatory network. The tumor-suppressive miR-4731-5p is significantly downregulated in stage IV metastatic melanoma compared to stage III. When overexpressed, miR-4731-5p reduces the expression of genes involved in melanosome function and cell cycle regulation, including RAB7A. As a direct target of miR-4731-5p, RAB7A inhibition leads to the downregulation of synovial sarcoma X chromosome breakpoint (SSX) family members—known promoters of melanoma growth. This results in reduced SSX4 protein levels and ultimately suppresses tumor cell colony formation [26].

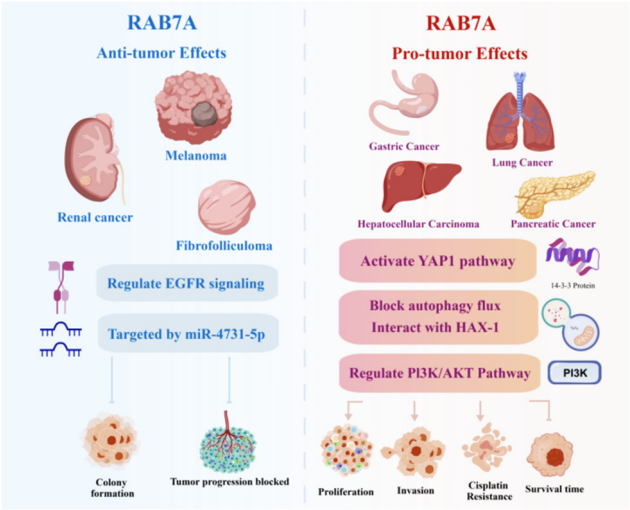


Figure 1. The Dual Roles of RAB7A in Tumorigenesis: Anti-tumor and Pro-tumor Effects and Underlying Mechanisms

In summary, RAB7A exhibits distinct and context-dependent roles in tumor development. Its function is shaped by multiple factors, including tumor type, upstream regulatory molecules, and downstream signaling networks. In most solid tumors, RAB7A promotes malignancy by regulating autophagy-lysosome function, activating oncogenic signaling pathways, and contributing to treatment

resistance. However, in specific settings, it can also suppress tumor growth by cooperating with tumor suppressors or by being regulated by tumor-suppressive miRNAs.

Notably, systematic research on RAB7A in OSCC remains limited. Given its diverse functions in other tumor types and the molecular characteristics of OSCC, it is plausible that RAB7A may be involved in complex regulatory networks during OSCC progression.

3. Research Progress of RAB7A in Oral Diseases

In chronic inflammatory oral conditions such as periodontitis, RAB7A-mediated autophagy-lysosome function is essential for maintaining local tissue homeostasis. Studies using clinical samples and animal models have consistently shown that both total RAB7A and its active form, GTP-RAB7A, are significantly reduced in periodontitis. This reduction leads to impaired autophagic flux [28].

Genetic evidence further supports the importance of RAB7A in oral health. Patients with Charcot-Marie-Tooth disease type 2B (CMT2B) who carry mutations in RAB7A often experience reduced oral sensation and recurrent traumatic ulcers. These clinical features highlight the role of RAB7A in maintaining oral mucosal integrity and facilitating tissue repair [29].

The core pathological feature of periodontitis is the progressive destruction of periodontal supporting tissues. Disruption of autophagic homeostasis is now considered a key driver of the persistent inflammatory response in this disease [30].

RAB7A plays a central role in regulating autophagosome-lysosome fusion and lysosomal transport [31]. Its function is tightly controlled by post-translational modifications, particularly ubiquitination, which determines its stability and activity. Studies have shown that in periodontitis, the expression of the deubiquitinase USP4 is significantly reduced. This leads to increased ubiquitination and inactivation of RAB7A, forming a USP4-RAB7A regulatory axis that exacerbates inflammatory damage through impaired autophagic homeostasis.

Under normal conditions, USP4 removes ubiquitin modifications from RAB7A, maintaining its activated state and ensuring proper lysosomal transport and autophagosome-lysosome fusion. This supports periodontal tissue homeostasis. In periodontitis, however, reduced USP4 expression weakens this effect. As a result, autophagic clearance becomes impaired, leading to the accumulation of damaged organelles, abnormal proteins, and pathogens. This triggers sustained release of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), ultimately contributing to the progressive destruction of periodontal tissues [28].

Notably, OSCC progression often occurs in the context of chronic oral inflammation, including periodontitis. Given that autophagic dysfunction and inflammatory microenvironment remodeling are hallmarks of OSCC malignancy, it is possible that RAB7A may promote OSCC progression through similar post-translational regulatory mechanisms.

RAB7A functions as a key molecular switch that regulates late endocytosis and autophagic pathways. Its activity is precisely controlled by a series of reversible post-translational modifications, forming a regulatory network that responds to cellular status. Among these modifications, sirtuin 5 (SIRT5)-mediated desuccinylation serves as a key positive regulatory mechanism. SIRT5 catalyzes the desuccinylation of RAB7A at lysine 31, which maintains its GTPase activity and promotes autophagosome-lysosome fusion. This ensures the normal operation of RAB7A and the complete execution of autophagic flux under physiological conditions [32].

In CMT2B, pathogenic missense mutations in RAB7A disrupt its function through a different mechanism [33]. Although these mutations do not directly alter covalent modifications, they reshape the protein conformation and interfere with the normal modification cycle and effector interactions. Specifically, they disrupt the binding balance with peripheral proteins, tropomyosin receptor kinase A (TrkA), and EGFR, leading to abnormal neurotrophic signaling and impaired receptor degradation [34]. In addition, these mutations reduce RAB7A localization in autophagic compartments and inhibit autophagic flux. This is accompanied by abnormal changes in lysosome number and activity, altered content of mitochondrial-derived vesicles (MDVs), and endothelial dysfunction. Together, these defects contribute to axonal degeneration and peripheral neuropathy [35].

These studies collectively demonstrate that maintaining the post-translational modification homeostasis of RAB7A is essential for the functional integrity of the endocytosis-autophagy-lysosome axis in neurons. Disruption of this modification network leads to protein homeostasis failure, which represents a common pathological basis for neurodegenerative diseases such as Alzheimer's disease (AD) and CMT2B. Notably, this functional regulatory logic based on RAB7A post-translational modifications may also have relevance for understanding the malignant progression of OSCC

4. Molecular Mechanisms of OSCC Cellularity and Development

The occurrence and progression of OSCC involves a complex network of multiple factors and disrupted molecular targets. A key driving force behind its malignant transformation is the loss of signaling pathway homeostasis [36]. Several major pathways, including Hippo/YAP, PI3K/AKT, mTOR, and MAPK, are frequently dysregulated in OSCC. Their abnormal activation or inhibition promotes tumor development through synergistic effects on cell proliferation, apoptosis escape, migration, invasion, and metabolic reprogramming.

4.1. PI3K/AKT Signaling Pathway: A Key Oncogenic Network Driving the Malignant Phenotype of OSCC

The PI3K/AKT signaling pathway is one of the most frequently dysregulated oncogenic networks in OSCC [37]. Its persistent activation is extensively involved in regulating tumor cell proliferation, apoptosis escape, invasion and metastasis, angiogenesis, and treatment resistance [38]. Studies have shown that phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene mutations, such as E545K and H1047R, are highly prevalent in various cancers, including breast, colorectal, and lung cancer. These mutations lead to sustained PI3K activation and promote tumor progression [39]. The activity of this pathway is influenced by both TME factors and epigenetic modifications. It also serves as a central hub that cross-talks

with multiple other oncogenic signaling pathways during OSCC malignant progression [40].

In OSCC, TNF-α in the inflammatory microenvironment can activate PI3K/AKT signaling and induce epithelial–mesenchymal transition (EMT) in OSCC cells. This leads to downregulation of E-cadherin and enhanced invasive and metastatic ability. Notably, the PI3K-specific inhibitor LY294002 can effectively reverse these effects [41]. In another example, the natural compound cardamonin has been shown to inhibit OSCC cell migration, proliferation, and invasion while inducing apoptosis. It does so by suppressing PI3K/AKT activation and downregulating matrix metalloproteinase 9 (MMP9) expression, highlighting the potential of natural compounds in OSCC treatment [42].

Notably, the PI3K/AKT pathway may have a potential regulatory link with RAB7A-mediated signaling. Existing evidence suggests that RAB7A can influence cell survival and metabolism by regulating AKT phosphorylation levels. Given that persistent AKT activation is a key driver of OSCC progression, this interaction may be clinically relevant [43]. In addition, bioinformatics analysis by Zhang et al. revealed that RAB7A is involved in somatic cell outer membrane degradation and PI3K/AKT activation in gastric cancer. This raises the possibility that RAB7A may similarly regulate PI3K/AKT activity and related cellular behaviors in OSCC [44]. Fibroblast growth factor 6 (FGF6) is another molecule of interest in this context. It is lowly expressed in OSCC tissues and exerts its effects by binding to fibroblast growth factor receptor 4 (FGFR4), thereby regulating both PI3K/AKT and MAPK signaling pathways [45]. FGF6 also inhibits ferroptosis in OSCC cells by modulating the expression of ferroptosis-related proteins, such as glutathione peroxidase 4 (GPX4) and acyl-CoA synthetase long-chain family member 4 (ACSL4), suggesting a tumor suppressive role [46]. Interestingly, studies have shown that RAB7 plays an essential role in FGF-dependent mesodermal patterning and left-right asymmetry establishment. Specifically, RAB7 functions upstream of MAPK-dependent mesodermal specification, most likely at the level of Ras activation [47].

Taken together, these findings point to a complex regulatory network involving RAB7A, OSCC, and the PI3K/AKT/MAPK signaling pathways. On one hand, the MAPK pathway is a key mediator of FGF6's tumor suppressive effects in OSCC. On the other hand, RAB7A is involved in FGF signal transduction and can regulate MAPK activity through upstream molecules such as Ras. Therefore, it is plausible that RAB7A may indirectly influence OSCC-related cellular behaviors—including proliferation, apoptosis, and ferroptosis—by modulating FGF-mediated PI3K/AKT or MAPK signaling

4.2. Hippo/YAP Signaling Pathway: A Core Pathway Regulating OSCC Proliferation, Drug Resistance and Immune Escape

The Hippo signaling pathway is an evolutionarily conserved regulator of cell proliferation and organ size. Its core function is to control the phosphorylation state, subcellular localization, and transcriptional activity of YAP and TAZ through a kinase cascade reaction [48]. In the OSCC TME, increased extracellular matrix (ECM) stiffness and changes in growth factors and cytokines can inactivate the Hippo pathway. This leads to the accumulation of YAP/TAZ in the nucleus, where they initiate the transcription of downstream oncogenes and promote tumor cell proliferation [49].

Once in the nucleus, YAP/TAZ bind to transcription factors such as TEAD and activate gene programs that drive cell proliferation, survival, stemness maintenance, and EMT. Importantly, aberrant YAP/TAZ activation has emerged as a central mechanism underlying treatment resistance in OSCC [50]. In the context of chemoresistance, YAP/TAZ enable cancer cells to evade the effects of drugs like cisplatin by enhancing DNA damage repair, upregulating multidrug resistance proteins, and inhibiting apoptotic pathways. In a related finding, Wu et al. reported that Hapalindole Q promotes the atypical degradation of YAP1 through chaperone-mediated autophagy. This compound also disrupts the normal distribution of RAB7 and inhibits autophagosome-lysosome fusion during macroautophagy [51], thereby suppressing OSCC progression.

4.3. mTOR Signaling Pathway: A Key Pathway Interacting with RAB7A to Regulate OSCC Metabolism and Survival

As the core effector of the PI3K/AKT/mTOR (PAM) signaling pathway, mTOR plays a key role in cancer. It regulates cancer development, metabolic reprogramming, and treatment resistance. mTOR functions by forming two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). When mTORC1 is activated, it promotes the synthesis of proteins, lipids, and nucleotides. At the same time, it inhibits autophagy. This provides cancer cells with the materials and energy they need for uncontrolled growth and survival. Meanwhile, mTORC2 strengthens cell survival signals. It also regulates kinases such as AKT, which contributes to EMT-related invasion and metastasis [39].

RAB7A becomes activated when it binds to GTP. In this state, it can directly interact with mTOR, the core subunit of mTORC1. This interaction typically depends on GTP binding. Functionally, RAB7A acts as a negative regulator of the mTORC1 pathway. It does so by blocking the recruitment of mTORC1 to the lysosomal membrane [52]. The GTP-binding ability of RAB7A mutants also influences mTORC1 activity. Differences in this ability directly affect how strongly mTORC1 is activated [53]. This suggests that the nucleotide-binding state of RAB7A is a key molecular switch. It enables precise control over mTORC1 signaling [54].

Taken together, these studies show that OSCC development is not driven by a single abnormal pathway. Instead, it results from the coordinated disruption of multiple oncogenic networks. These include the Hippo/YAP [55], PAM [56], and MAPK [57] pathways. They act together within a specific tumor microenvironment. These pathways are highly interconnected. They jointly regulate critical processes such as tumor cell proliferation, invasion, and metastasis. They also control metabolic reprogramming and immune escape[58]. Their activity is influenced by classic ligand-receptor signals. It also depends on precise regulation by intracellular homeostatic systems[59]. However, it remains unclear how the autophagic machinery functionally links with these classic oncogenic pathways in OSCC.

RAB7A is a core small GTPase. It is involved in late endosome maturation, autophagosome-lysosome fusion, and lysosome function. Recent studies have linked RAB7A to tumor progression, invasion and metastasis, and treatment resistance in various solid tumors.OSCC is a malignancy that heavily depends on metabolic adaptation and signal integration[60]. Therefore, it is important to systematically

characterize the expression patterns and molecular mechanisms of RAB7A in this cancer type. Such efforts could help refine current models of OSCC pathogenesis. They may also pave the way for new diagnostic and therapeutic strategies.

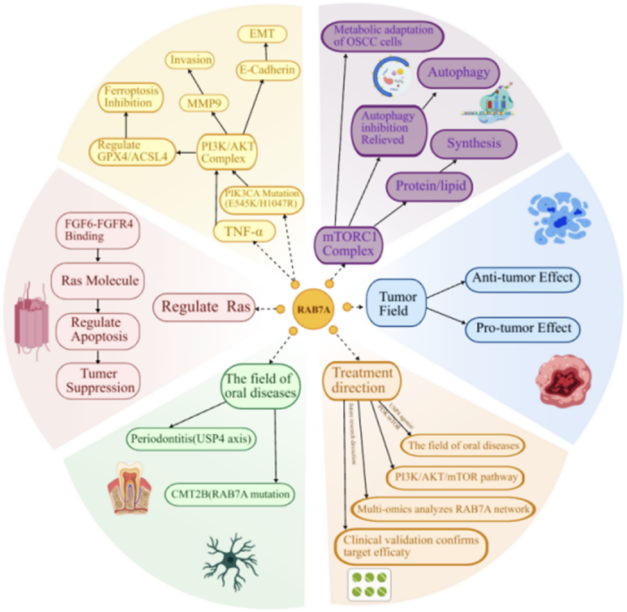


Figure 2. A comprehensive schematic of RAB7A's functions in oral squamous cell carcinoma, oral diseases, and translational research directions

5. Conclusion and Prospect

RAB7A is a key hub molecule connecting the endocytosis-autophagy-lysosome system with multiple oncogenic signaling pathways. In the field of oncology, the pro-malignant effect of RAB7A is universal across cancer types. In solid tumors such as pancreatic cancer and liver cancer, it drives tumor proliferation, invasion and metastasis, and poor prognosis through mechanisms such as regulating autophagic flux, mediating treatment resistance, and activating oncogenic signaling pathways, and its functional diversity and signal network integration ability have been fully confirmed. As the most common malignant tumor of the oral cavity, the progression of OSCC depends on the synergistic disorder of multiple signaling pathways such as Hippo/YAP, PI3K/AKT/mTOR and MAPKand these pathways have a close functional coupling with the autophagic system, providing a clear mechanistic entry point for RAB7A to participate in the pathological process of OSCC.

Existing studies have preliminarily shown that RAB7A is a central hub linking the autophagy-lysosome system with oncogenic signaling. It is closely associated with the occurrence, progression, malignant evolution, and treatment response of OSCC. However, the specific mechanisms, regulatory networks, and clinical translational value remain underexplored. Future research should first clarify the core functional role of RAB7A in OSCC. Specifically, it remains unknown whether RAB7A acts as a pro-tumor factor to promote proliferation, invasion, and metastasis. Alternatively, it may exert tumor-suppressive effects in specific subgroups or microenvironments. Another possibility is a temporally and spatially dependent functional switch. Regarding molecular mechanisms, attention should be paid to the upstream and downstream molecular networks of RAB7A in OSCC. Key upstream regulators, such as transcription factors and non-coding RNAs, should be identified. Downstream effector proteins also need to be characterized. This will help establish a comprehensive RAB7A-mediated signaling network in OSCC.For clinical application, large-scale clinical samples should be used for validation. These include OSCC tissues, adjacent normal tissues, peripheral blood, and saliva. The expression characteristics and clinical relevance of RAB7A must be assessed. Specifically, it is important to determine whether RAB7A expression is significantly elevated in OSCC tissues compared with adjacent normal tissues. Its correlation with clinical stage, pathological grade, lymph node metastasis, and patient survival should also be evaluated.

In summary, future research should integrate multi-omics analysis, functional assays, and clinical sample validation. This will allow a thorough dissection of the regulatory network of RAB7A in OSCC. Such efforts are expected to provide new theoretical foundations and potential therapeutic targets for precision diagnosis and treatment of OSCC.

Acknowledgments

This study was supported by the scientific research funds from the Science Research Project of Hebei Education Department (NO. QN2026745) and the Innovation and Entrepreneurship Program for College Students in Hebei Province (S202510081062).

References

[1] Langemeyer L, Fröhlich F, Ungermann C. Rab GTPase function in endosome and lysosome biogenesis[J]. Trends in Cell Biology, 2018, 28(11): 957-970.

[2] Hewawasam NV, Lhaf F, Taylor HA, Viloria K, Austin A, King A, Jones P, Jones L, Turner MD, Hill NJ. Modulation of Rab7a-mediated growth factor receptor trafficking inhibits islet beta cell apoptosis and autophagy under conditions of metabolic stress. Sci Rep. 2020 Sep 25;10(1):15741.

[3] Bhattacharya A, Mukherjee R, Kuncha S K, et al. A lysosome membrane regeneration pathway depends on TBC1D15 and autophagic lysosomal reformation proteins[J]. Nature Cell Biology, 2023, 25(5): 685-698.

[4] Zhang K, Chowdary P D, Cui B. Visualizing directional Rab7 and TrkA cotrafficking in axons by pTIRF microscopy[J]. Methods in Molecular Biology, 2015, 1298: 319-329.

[5] Badwelan M, Muaddi H, Ahmed A, et al. Oral squamous cell carcinoma and concomitant primary tumors, what do we know? A review of the literature[J]. Current Oncology, 2023, 30(4): 3721-3734.

[6] Tan Y, Wang Z, Xu M, et al. Oral squamous cell carcinomas: state of the field and emerging directions[J]. International Journal of Oral Science, 2023, 15(1): 44.

[7] Gan M, Liu N, Li W, et al. Metabolic targeting of regulatory T cells in oral squamous cell carcinoma: new horizons in immunotherapy[J]. Molecular Cancer, 2024, 23(1): 273.

[8] Arora R, Cao C, Kumar M, et al. Spatial transcriptomics reveals distinct and conserved tumor core and edge architectures that predict survival and targeted therapy response[J]. Nature Communications, 2023, 14(1): 5029.

[9] Zhou J, Hu Z, Wang L, et al. Tumor-colonized Streptococcus mutans metabolically reprograms tumor microenvironment and promotes oral squamous cell carcinoma[J]. Microbiome, 2024, 12(1): 193.

[10] Dong L, Hu S, Li X, et al. SPP1+ TAM regulates the metastatic colonization of CXCR4+ metastasis-associated tumor cells by

remodeling the lymph node microenvironment[J]. Advanced Science, 2024, 11(44): e2400524.

[11] Sun J, Tang Q, Yu S, et al. F. nucleatum facilitates oral squamous cell carcinoma progression via GLUT1-driven lactate production[J].

[12] Franken A, Bila M, Mechels A, et al. CD4+ T cell activation distinguishes response to anti-PD-L1+anti-CTLA4 therapy from anti-PD-L1 monotherapy[J]. Immunity, 2024, 57(3):

[13] Ju W T, Xia R H, Zhu D W, et al. A pilot study of neoadjuvant combination of anti-PD-1 camrelizumab and VEGFR2 inhibitor apatinib for locally advanced resectable oral squamous cell carcinoma[J]. Nature Communications, 2022, 13 (1): 5378.

[14] Tang S, Wang Q, Wang Z, et al. NSD1 mutation status determines metabolic inhibitor sensitivity in head and neck squamous cell carcinomas by regulating mitochondrial respiration[J]. The Journal of Pathology, 2025, 266(3): 306-321.

[15] Chen Y, Li Z, Liang J, Liu J, Hao J, Wan Q, Liu J, Luo C, Lu Z. CircRNA has_circ_0069313 induced OSCC immunity escape by miR-325-3p-Foxp3 axes in both OSCC cells and Treg cells[J]. Aging (Albany NY), 2022, 14(10): 4376-4389

[16] Shebbo S, Alateyah N, Yassin E, et al. Unravelling molecular mechanism of oral squamous cell carcinoma and genetic landscape: an insight into disease complexity, available therapies, and future considerations[J]. Frontiers in Immunology, 2025, 16: 1626243.

[17] Liu Q. Expression of RAB7A in pancreatic cancer and its clinical significance[D]. 2023.

[18] Ding N, Bai Q, Wang Z, Piao Y, Li L, Piao H, Yan G, Song Y. Artemetin targets the ABCG2/RAB7A axis to inhibit mitochondrial dysfunction in asthma[J]. Phytomedicine, 2025, 140: 156600.

[19] Zhou B, Liu J, Kang R, et al. Ferroptosis is a type of autophagy-dependent cell death[J]. Seminars in Cancer Biology, 2020, 66:89-100.

[20] Zhou C, Liang Y, Zhou L, Yan Y, Liu N, Zhang R, Huang Y, Wang M, Tang Y, Ali DW, Wang Y, Michalak M, Chen XZ, Tang J. TSPAN1 promotes autophagy flux and mediates cooperation between WNT-CTNNB1 signaling and autophagy via the MIR454-FAM83A-TSPAN1 axis in pancreatic cancer[J]. Autophagy, 2021, 17(10): 3175-3195.

[21] Zhang J Y. Research on the role and molecular mechanism of RAB7A, a downstream gene of ATF6, in regulating the progression of hepatocellular carcinoma[D]. 2024.

[22] Zhang S Y, You B, You Y W. HAX-1 participates in cisplatin resistance of nasopharyngeal carcinoma by competitively binding to Rab7a to block autophagic flux[C]2021: 456-457.

[23] Wang L L. Research on the mechanism of enhancing the sensitivity of lung cancer to gemcitabine by knocking out RAB7A based on CRISPR/Cas9 technology[D]. 2024.

[24] Xu F Y, Liu R, Ma L, et al. Network analysis of Rab7a gene in breast cancer MDA-MB-231 cells[J].2020, 46(3): 464-469-671.

[25] LLaviolette L A, Mermoud J, Calvo I A, et al. Negative regulation of EGFR signalling by the human folliculin tumour suppressor protein[J]. Nature Communications, 2017, 8(1): 15866.

[26] Stark M S, Tom L N, Boyle G M, et al. The "melanoma-enriched" microRNA miR-4731-5p acts as a tumour suppressor[J]. Oncotarget, 2016, 7(31): 49677-49687.

[27] Güleç Taşkiran A E, Hüsnügil H H, Soltani Z E, et al. Post-transcriptional regulation of Rab7a in lysosomal positioning and drug resistance in nutrient-limited cancer cells[J]. Traffic, 2024, 25(9): e12956.

[28] Kang S, Liu S, Dong X, et al. USP4 depletion-driven RAB7A ubiquitylation impairs autophagosome-lysosome fusion and aggravates periodontitis[J]. Autophagy, 2025, 21(4): 771-788.

[29] Liu H, Wu C. Charcot Marie Tooth 2B peripheral sensory neuropathy: How Rab7 mutations impact NGF signaling?[J]. International Journal of Molecular Sciences, 2017, 18(2): 324.

[30] Chen L, Hu P, Hong X, et al. Dimethyl fumarate modulates M1/M2 macrophage polarization to ameliorate periodontal destruction by increasing TUFM-mediated mitophagy[J]. International Journal of Oral Science, 2025, 17(1): 32..

[31] Rahman M A, Shaikh M H, Gupta R D, et al. Advancements in autophagy modulation for the management of oral disease: A focus on drug targets and therapeutics[J]. Biomedicines, 2024, 12(11): 2645.

[32] Deng P, Fan T, Gao P, et al. SIRT5-mediated desuccinylation of RAB7A protects against cadmium-induced Alzheimer's disease-like pathology by restoring autophagic flux[J]. Advanced Science, 2024, 11(30): e2402030.

[33] Romano R, Del Fiore V S, Saveri P, et al. Autophagy and lysosomal functionality in CMT2B fibroblasts carrying the RAB7K126R mutation[J]. Cells, 2022, 11(3): 496.

[34] Mulligan R J, Winckler B. Regulation of endosomal trafficking by Rab7 and its effectors in neurons: Clues from Charcot-Marie-Tooth 2B disease[J]. Biomolecules, 2023, 13(9): 1399.

[35] Girolimetti G, Marini F, Calvani R, et al. Circulating mitochondrial components and metabolic and inflammatory markers in Charcot-Marie-Tooth type 2B[J]. Neurobiology of Disease, 2025, 214: 107051.

[36] Bugshan A, Farooq I. Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis[J]. F1000Res, 2020, 9: 229.

[37] Veerasamy V, Veeran V, Nagini S. Dysregulated PI3K/AKT signaling in oral squamous cell carcinoma: The tumor microenvironment and epigenetic modifiers as key drivers[J]. Oncology Research, 2025, 33(8): 1835-1860.

[38] Harrison MS, Hung CS, Liu TT, Christiano R, Walther TC, Burd CG. A mechanism for retromer endosomal coat complex assembly with cargo[J]. Proc Natl Acad Sci U S A, 2014, 111(1): 267-272.

[39] Glaviano A, Foo A S C, Lam H Y, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer[J]. Molecular Cancer, 2023, 22(1): 138.

[40] Zhao X W, Zhou J P, Bi Y L, et al. The role of the PI3K/AKT signaling pathway in promoting the invasion and metastasis of oral squamous cell carcinoma[J]. 2019, 38(1): 75-79.

[41] Li Y F. Research on the molecular mechanism of PKM2-mediated HMGB1 regulation of TAMs promoting the migration and invasion of oral squamous cell carcinoma[D]. 2025.

[42] Wu Y, Wang Y, Liu H, et al. Mechanism of apoptosis in oral squamous cell carcinoma promoted by cardamonin through PI3K/AKT signaling pathway[J]. Scientific Reports, 2024, 14(1): 20802.

[43] Romano R, Calcagnile M, Margiotta A et al. RAB7A regulates vimentin phosphorylation through AKT and PAK[J]. Cancers, 2021, 13(9): 2164.

[44] Zhang M, Liu S, Zhang N, et al. High expression of RAB7A is associated with poor prognosis of gastric cancer by promoting tumor invasion[J]. 2023, 43(10): 1734-1743.

[45] Bala M, CD S, TML M, et al. Expression of FGF-2/FGFR-1 in normal mucosa, salivary gland, preneoplastic, and neoplastic lesions of the oral cavity[J]. Journal of Oral Pathology & Medicine, 2018, 47(9): 821-828.

[46] Zhang X, Xu Y, Shi L, et al. FGF6 inhibits oral squamous cell carcinoma progression by regulating PI3K/AKT and MAPK pathways[J]. Scientific Reports, 2024, 14(1): 2687.

[47] Kreis J, Camuto C M, Elsner C C, et al. FGF-mediated establishment of left-right asymmetry requires Rab7 function in the dorsal mesoderm in Xenopus[J]. Frontiers in Cell and Developmental Biology, 2022, 10: 981762.

[48] Sa P, Singh P, Panda S, et al. Reversal of cisplatin resistance in oral squamous cell carcinoma by piperlongumine loaded smart nanoparticles through inhibition of Hippo-YAP signaling pathway[J]. Translational Research, 2024, 268: 101664.

[49] Hasegawa K, Fujii S, Matsumoto S, et al. YAP signaling induces PIEZO1 to promote oral squamous cell carcinoma cell proliferation[J]. The Journal of Pathology, 2021, 253(1): 80-93.

[50] Gupta A, Devi A, Kamboj M, et al. Immunohistochemical expression of PARK2 and YAP in oral epithelial dysplasia and oral squamous cell carcinoma[J]. Head and Neck Pathology, 2025, 19(1): 112-120.

[51] Wu Y, Wang S, Guo Z, et al. Hapalindole Q suppresses autophagosome-lysosome fusion by promoting YAP1 degradation via chaperon-mediated autophagy[J]. Proceedings of the National Academy of Sciences, 2024, 121(50): e2400809121.

[52] Lin J X, Xu C Y, Wu X M, et al. Rab7a-mTORC1 signaling-mediated cholesterol trafficking from the lysosome to mitochondria ameliorates hepatic lipotoxicity induced by aflatoxin B1 exposure[J]. Chemosphere, 2023, 320: 138071.

[53] Akula SM, Abrams SL, Steelman LS, Emma MR, Augello G, Cusimano A, Azzolina A, Montalto G, Cervello M, McCubrey JA. RAS/RAF/MEK/ERK, PI3K/PTEN/AKT/mTORC1 and TP53 pathways and regulatory miRs as therapeutic targets in hepatocellular carcinoma[J]. Expert Opin Ther Targets, 2019, 23(11): 915-929.

[54] Song J R. Research on the mechanism by which TTPA and Rab7A affect HBV replication through activating the mTORC1 signaling pathway[D]. 2020.

[55] Amano Y, Matsubara D, Kihara A, et al. The significance of Hippo pathway protein expression in oral squamous cell carcinoma[J]. Frontiers in Medicine, 2024, 11: 1247625.

[56] Benitha J G, Ramani P, Jayaraman S, et al. Role of PDGF-BB in oral squamous cell carcinoma through PI3/AKT/mTOR pathway: An integrated computational and Real-Time PCR-Based Approach[J]. Asian Pacific Journal of Cancer Prevention, 2026, 27(1): 109-116.

[57] Wei L J, Zhang M Y. Study on the effect of AAVC-I on inhibiting the proliferation and migration of human oral squamous cell carcinoma SCC4 and Cal27 cells through the ERK1/2/MAPK signaling pathway[J]. 2025, 30(11): 1516-1524.

[58] Rajendran P, Sekar R, Dhayasankar P S, et al. PI3K/AKT signaling pathway mediated autophagy in oral carcinoma - A comprehensive reviewJ[J]. International Journal of Medical Sciences, 2024, 21(6): 1165-1175.

[59] Hsu P C, Tsai C, Lin Y H, et al. Therapeutic targeting of apoptosis, autophagic cell death, necroptosis, pyroptosis, and ferroptosis pathways in oral squamous cell carcinoma: molecular mechanisms and potential strategies[J]. Biomedicines, 2025, 13(7): 1745.

[60] Modica G, Tejeda-Valencia L, Sauvageau E, Yasa S, Maes J, Skorobogata O, Lefrancois S. Phosphorylation on serine 72 modulates Rab7A palmitoylation and retromer recruitment[J]. J Cell Sci, 2025, 138(1): jcs262177.