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Progress in Scaffold Proteins in Oral Squamous Cell Carcinoma: Mechanisms and Therapeutic Implications

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Abstract. Oral squamous cell carcinoma (OSCC) remains a major global health burden with limited improvement in long-term survival, largely due to late diagnosis and an incomplete understanding of its underlying mechanisms. Emerging evidence indicates that chronic mechanical irritation (CMI), a unique physical stimulus in the oral cavity, plays a critical role in OSCC initiation and progression by synergizing with classical risk factors such as tobacco, alcohol, and high-risk HPV infection. CMI contributes to extracellular matrix (ECM) remodeling and increased matrix stiffness, thereby activating mechanotransduction pathways including the Hippo-YAP/TAZ axis and calcium influx mediated by mechanosensitive channels such as PIEZO1 and TRPV4. These signals are further integrated and amplified by scaffold proteins, which function as spatiotemporal organizers of signaling complexes. Scaffold proteins, exemplified by focal adhesion kinase (FAK) and paxillin, serve as key mediators linking the mechanical microenvironment to intracellular oncogenic signaling, promoting proliferation, invasion, epithelial–mesenchymal transition, and therapeutic resistance in OSCC. Notably, the HOMER protein family, particularly HOMER3, has emerged as a potential regulator of calcium signaling microdomains and tumor progression, although its role in OSCC remains largely unexplored. This review systematically summarizes the CMI–ECM remodeling–mechanotransduction–scaffold protein regulatory axis in OSCC and highlights the potential of HOMER3 as a novel biomarker and therapeutic target. These insights provide a comprehensive framework for understanding OSCC pathogenesis and may facilitate the development of precision diagnostic and therapeutic strategies.

Keywords: Oral squamous cell carcinoma, Scaffold proteins, Chronic mechanical irritation, Mechanotransduction, HOMER3

1. Introduction

Oral cancer refers to a group of malignant tumors occurring in the lips and oral cavity. Since more than 90% of oral malignant tumors histologically derive from squamous epithelial cells, oral cancer has traditionally been specifically referred to as oral squamous cell carcinoma [1]. Globally, there are approximately 350,000 to 360,000 new cases of Oral squamous cell carcinoma (OSCC) each year. Head and neck squamous cell carcinoma, which includes OSCC, ranks the eighth among all

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malignant tumors worldwide in terms of new cases. The five-year survival rate of OSCC patients remains between 40% and 50%, with no remarkable breakthrough improvement in recent years [2]. This disease predominantly affects adults aged 40 to 60 years old, and the incidence rate in males is about two to three times that in females. This discrepancy is presumed to be closely associated with higher tobacco consumption and more frequent alcohol drinking among males [1, 3]. Multiple types of oral squamous cell carcinoma, such as tongue cancer, gingival cancer and floor-of-mouth cancer, are prone to early lymph node metastasis and progress rapidly [4]. In addition, the five-year survival rate of patients who receive primary radical surgery for OSCC is strongly correlated with tumor staging. The five-year survival rate reaches 71.8% for patients at early stages, while it drops to 51.0% for those at advanced stages [5]. Therefore, early detection and early treatment are essential to improve the five-year survival rate of patients.

Clinically, however, most patients do not present obvious precancerous lesions before being diagnosed with advanced HNSCC [6]. Hence, exploring relevant carcinogenic factors is of great significance for the prevention of OSCC among high-risk populations and timely identification of potential lesions by clinicians. Current etiological studies on OSCC have confirmed three classic carcinogenic factors, namely tobacco exposure, excessive alcohol intake and high-risk HPV infection [7]. Furthermore, previous domestic and overseas studies have demonstrated that chronic mechanical irritation (CMI), such as long-term friction and stimulation on oral mucosa, has a strong and statistically significant correlation with the onset of oral cancer. Nevertheless, CMI is more likely to act as a potential co-factor rather than an independent risk factor for carcinogenesis [8, 9]. This paper mainly focuses on mechanical factors, reviews previous relevant studies, summarizes how CMI interacts with other carcinogenic factors at the molecular signaling pathway level to elevate canceration risk and accelerate disease progression, and puts forward prospects for future research.

2. Clinical correlation between CMI and OSCC

CMI induces changes in certain biomarkers similar to those observed in OSCC, including Ki67 and Ck19 [10]. A latest study has further found that CMI can promote epigenetic modifications such as gene methylation, which reduces the expression levels of tumor suppressor proteins and DNA repair proteins including p16 and MGMT, and consequently drives carcinogenesis [11]. Moreover, among people who smoke and drink alcohol, CMI can further enhance the carcinogenic effects of tobacco and alcohol [12]. As early as the 1980s, researchers established animal models to verify the relationship between CMI and oral leukoplakia. Single CMI could induce simple mucosal leukoplakia, which was characterized by mild epithelial hyperplasia and hyperkeratosis in the early phase. Lesions aggravated with increased stimulation frequency, yet the overall pathological changes remained mild without obvious atypical hyperplasia. Stimulation with simple tobacco and alcohol extract could lead to palatal mucosal leukoplakia with severer lesions than those caused by mechanical irritation alone, accompanied by epithelial hyperplasia, dyskeratosis and focal atypical hyperplasia in individual cases. Single nicotine stimulation resulted in even more serious pathological changes. When combined stimulation was applied, the induced leukoplakia lesions were far severer than those caused by any single stimulus. After the termination of stimulation, the leukoplakia lesions in experimental animals failed to subside in a short period of time [9]. Oral Leukoplakia (OL) is recognized as one of the most common precancerous lesions. One out of every ten OSCC cases develops from oral leukoplakia, and malignant transformation may occur within three months after the diagnosis of leukoplakia [13]. Accordingly, it can be inferred that CMI creates

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a favorable microenvironment for the occurrence and development of OSCC and increases the risk of malignant transformation.

Taking tongue cancer as an example, over half of its cases occur at the lateral margin of the middle one-third of the tongue, followed by the ventral and dorsal sides of the tongue. Due to anatomical adjacency, chronic mechanical irritation to the tongue caused by sharp cusps, residual tooth roots and ill-fitting prostheses is undoubtedly a major pathogenic factor for tongue cancer. In addition, the lateral margin of the tongue is rich in lymphatic networks with bilateral lymphatic drainage, mainly to submandibular, submental and upper deep cervical lymph nodes. This leads to a high rate of early cervical lymph node metastasis and relatively poor prognosis [14].

In conclusion, as a critical physical stimulating factor, chronic mechanical irritation (CMI) can directly induce precancerous lesions such as oral leukoplakia, amplify carcinogenic risks synergistically with physical and chemical stimuli like tobacco and alcohol, and serve as a key pathogenic inducer for site-specific oral squamous cell carcinoma represented by tongue cancer (Table 1).

Table 1. Clinical and biological evidence linking chronic mechanical irritation (CMI) to oral squamous cell carcinoma

Study/Reference	Experimental or Clinical Model	Main Findings	Implications for OSCC
Piemonte et al., 2018 [8]	Systematic review and meta-analysis	Chronic mechanical irritation showed a significant statistical association with OSCC occurrence	CMI may act as a co-carcinogenic factor in oral carcinogenesis
Piemonte et al., 2010 [12]	Case-control study	CMI enhanced the carcinogenic effects of tobacco and alcohol	Mechanical stimulation synergizes with classical carcinogens
Chronic traumatic ulcer studies [10]	Clinical and immunohistochemical analysis	Increased Ki67 and CK19 expression in chronic traumatic ulcers	CMI lesions share proliferative features with OSCC
Deboni et al., 2019 [11]	Epigenetic analysis of chronic traumatic ulcers	Hypermethylation of p16 and MGMT observed in chronic ulcers	CMI may promote epigenetic dysregulation during malignant transformation
Animal model study [9]	Rat palatal mucosa stimulation model	Combined mechanical, tobacco and alcohol stimulation induced more severe leukoplakia-like lesions	CMI contributes to oral premalignant lesion progression
Neville and Day, 2002 [13]	Clinical review	Oral leukoplakia is one of the most common oral premalignant lesions	CMI-associated leukoplakia may increase OSCC risk

3. Changes in structure and stiffness of ECM in OSCC and precancerous lesions

The extracellular matrix (ECM) is a highly dynamic structure widely present in all tissues and constantly undergoing regulated remodeling. This process involves quantitative and qualitative alterations of the ECM, which are modulated by specific enzymes mediating ECM degradation such as Matrix Metalloproteinases (MMPs) [15]. Most cancer cells reside in an abnormally altered extracellular microenvironment, typically characterized by increased ECM stiffness and abnormal soluble signals composed of growth factors and cytokines. Cells sense the microenvironment not only through soluble signals like growth factors and cytokines, but also through physical and mechanical cues, such as ECM stiffness or restricted adhesion status. Cells then respond to microenvironmental changes, convert ECM stiffness and other mechanical alterations into

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biochemical signals, and regulate cell proliferation, differentiation, and even accelerate carcinogenesis [16]. Notably, the abnormally elevated ECM stiffness in the tumor microenvironment not only acts as a barrier to hinder drug delivery, but also activates cell membrane receptors and mechanical sensors by inducing mechanical stimulation, thereby further promoting tumor progression. In-depth exploration of the regulatory effects of ECM stiffness on tumor progression, including its impacts on tumor cell proliferation, migration, metastasis, drug resistance, angiogenesis, epithelial-mesenchymal transition, immune escape, stemness, metabolic reprogramming and genomic stability, is of great significance for identifying potential therapeutic targets for tumors. Therapeutic strategies targeting ECM stiffness and their influences on tumor progression have also become major research directions in related fields [17].

4. Mechanosensitive signal transduction in OSCC

As a crucial mechanical signal, ECM stiffness regulates tumor progression mainly relying on mechanosensitive signal transduction pathways. Specifically, cells perceive abnormal changes in ECM stiffness via mechanical sensors and receptors on the cell membrane, convert mechanical stimuli into intracellular biochemical signals, and further modulate various malignant phenotypes of tumor cells. Among relevant molecules, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) serve as one of the core transcriptional hubs that transform mechanical signals into cellular behaviors [18]. The conventional process is described as follows: cells perceive mechanical signals of ECM stiffening → the intracellular Hippo pathway is inactivated, accompanied by the deactivation of Large tumor suppressor kinase 2 (LATS2) → LATS2 normally phosphorylates YAP/TAZ to keep them inactive, and this inhibitory effect is subsequently eliminated → YAP/TAZ are dephosphorylated and activated, then translocate into the nucleus → nuclear YAP/TAZ specifically bind to TEA domain transcription factor 4 (TEAD4) to form the YAP-TEAD4 transcriptional complex, which gains the capacity to initiate the transcription of target genes → the YAP-TEAD4 complex stably binds to the regulatory sites of the PIEZO1 gene → transcription of the PIEZO1 gene is initiated → PIEZO1 mRNA enters the cytoplasm and is translated into abundant PIEZO1 protein → newly synthesized PIEZO1 protein is embedded into the cell membrane, greatly increasing the number of PIEZO1 channels on the membrane, which function as channels for extracellular calcium ions to flow into cells → extracellular calcium ions flow massively into the cytoplasm through PIEZO1 channels along the concentration gradient → Extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (p38 MAPK) are phosphorylated and activated → activated MAPK signals translocate into the nucleus and trigger the expression of genes related to cell proliferation. Transient receptor potential vanilloid 4 (TRPV4) is also an effector protein downstream of YAP/TAZ and shares similar functions with PIEZO1 [16]. A study published in Nature in 2011 reported a novel regulatory mechanism of YAP/TAZ independent of the Hippo pathway. Briefly, ECM stiffness ultimately affects the contractile tension of the cytoskeleton and controls the nuclear import and export of YAP/TAZ [18]. Nevertheless, the two pathways eventually lead to the same outcome, and calcium influx plays a pivotal bridging role throughout the process.

In summary, abnormally increased ECM stiffness and chronic mechanical stimulation-mediated mechanosensitive signal transduction constitute one of the core mechanisms driving the occurrence, proliferation, invasion and metastasis of OSCC. Downstream signaling axes including Hippo-YAP and PIEZO1-calcium influx-MAPK jointly form the core molecular network governing mechanical force regulation in OSCC. It is worth mentioning that the entire process of mechanical signal transmission, from extracellular sensing, intracellular transduction to cascade amplification, does not

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rely on random collision or non-specific binding of signaling molecules. Instead, it is precisely coordinated and regulated in both temporal and spatial dimensions by a group of molecules known as scaffold proteins (Table 2). On this basis, this paper further elaborates the core biological functions of scaffold proteins, and summarizes their roles and research advances in tumors, especially in the development and progression of OSCC (Figure 1).

Table 2. Major mechanotransduction-associated signaling pathways and scaffold proteins involved in OSCC progression

Molecule/Pathway	Biological Function	Mechanistic Role in OSCC	Representative References
ECM stiffness	Mechanical cue sensing	Promotes malignant transformation, invasion, EMT, and therapeutic resistance	[15, 17]
YAP/TAZ	Mechanosensitive transcriptional coactivators	Transduce ECM stiffness into transcriptional programs promoting proliferation and migration	[16]
PIEZO1	Mechanosensitive calcium channel	Mediates calcium influx and activates MAPK signaling	[16]
TRPV4	Mechanosensitive calcium channel	Functions downstream of YAP/TAZ and regulates mechanosensitive calcium signaling	[16]
FAK	Scaffold protein and tyrosine kinase	Regulates focal adhesion dynamics, invasion, survival, and anoikis resistance	[20–25]
Paxillin	Focal adhesion scaffold protein	Enhances migration, invasion, chemoresistance, and EMT	[26–28]
CAF-derived LOX-rich sEVs	ECM remodeling factor	Induces collagen crosslinking and ECM stiffening	[28]
MAPK/ERK signaling	Downstream proliferative signaling	Activated by mechanosensitive calcium influx	[16]
Arp2/3 complex	Cytoskeleton remodeling	Controls lamellipodia formation and cell migration downstream of FAK	[24]

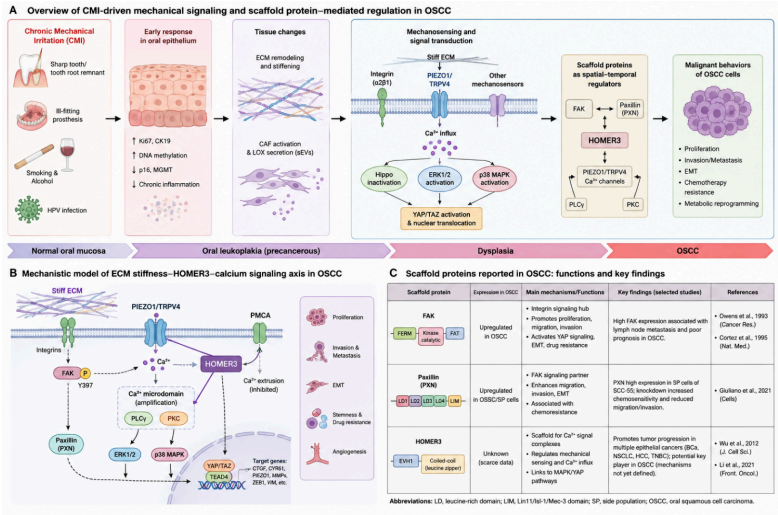

Figure 1. CMI-driven mechanotransduction and scaffold protein-mediated regulation in OSCC

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5. Biological functions of scaffold proteins and their roles in tumors

Scaffold proteins are a group of proteins containing multiple protein-protein interaction domains. They can bind to two or more components in signaling pathways simultaneously, assemble these components into complexes, and improve the efficiency and specificity of signal transduction. Most scaffold proteins have no intrinsic enzymatic activity and mainly function as molecular platforms [20]. Nevertheless, with the in-depth research on cellular signal transduction mechanisms, this traditional definition can no longer fully reflect the actual functions of scaffold proteins. Modern studies have confirmed that scaffold proteins are not merely involved in passive assembly. Instead, relying on their modular domains, they precisely regulate the assembly of signaling complexes in temporal and spatial dimensions. They act as placemakers that determine the location of signal activation and pacemakers that control the initiation and rhythm of signals, and actively define signal specificity, signal intensity and cell fate [19]. For instance, in non-immune cells, the scaffold protein AHNAK utilizes its multi-domain modular structure to anchor three core functional components of the calcium signaling cascade at the same time: cell membrane calcium channels that mediate calcium influx, including mechanosensitive calcium channels such as PIEZO1 and TRPV4, phospholipase Cγ (PLCγ), and protein kinase C (PKC) [21-23]. Since intracellular calcium ions are rapidly eliminated by highly expressed calcium-binding proteins after entering the cytoplasm, coupling calcium influx with major calcium effector molecules plays a vital role in amplifying signal transduction triggered by transient and weak calcium influx [23].

As research advances, the roles of scaffold proteins in tumors have been gradually uncovered. By mediating protein interactions via multiple domains and achieving spatiotemporally specific and precise regulation of signaling pathways, scaffold proteins serve as core regulatory molecules for malignant biological behaviors of tumor cells. Focal adhesion kinase (FAK) is a classic molecule with both kinase activity and scaffold function, and research on its functions and mechanisms in tumors has long been a hot topic in this field [19].

As early as 1993, researchers first detected abnormally high expression of FAK mRNA in invasive and metastatic tumor specimens from clinical samples. They initially proposed the core viewpoint that FAK overexpression is correlated with tumor invasive potential, which pioneered the research of FAK in oncology. A large-sample clinical study conducted in 1995 further verified this conclusion systematically at the protein level. It clarified that high FAK expression is a common feature of malignant progression in both epithelial and mesenchymal tumors, and FAK can act as a potential biomarker for tumor invasive capacity. These findings laid a solid clinical foundation for subsequent exploration of the regulatory roles of FAK as a scaffold protein in tumors [24, 25]. Follow-up studies revealed that FAK functions both as a scaffold protein and a tyrosine kinase. It consists of a kinase domain and a FERM (four-point-one, ezrin, radizin, moesin) domain, and the interaction between these two domains maintains FAK in an autoinhibitory state. The binding of phosphatidylinositol 4, 5-bisphosphate on the cell membrane to the FERM domain relieves autoinhibition, which induces autophosphorylation at the Y397 site of FAK. Subsequently, Src tyrosine kinase is recruited to phosphorylate FAK at Y576 and Y577, leading to full activation of FAK [26, 27]. Notably, phosphorylation at Y397 causes Arp2/3 to dissociate from FAK and detach from focal adhesions. Arp2/3 then relocates to lamellipodia and cellular protrusions where cells extend outward [28]. In addition, FAK participates in the ubiquitination and degradation of p53 [29]. The above evidence indicates that FAK promotes malignant phenotypes of tumors through two coordinated pathways: enhancing the migration, invasion and metastasis abilities of tumor cells, as well as driving uncontrolled cell proliferation and resistance to apoptosis.

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In conclusion, scaffold proteins do not only act as passive molecular scaffolds for signal assembly. They also actively and precisely regulate the intensity, specificity and biological effects of signal transduction in temporal and spatial dimensions. Typical scaffold proteins represented by FAK have been proven to have a close correlation between abnormal overexpression and malignant phenotypes such as tumor invasion and metastasis, and they exert essential regulatory effects on the development and progression of solid tumors. Current studies mainly focus on the shared oncogenic mechanisms of scaffold proteins in various solid tumors throughout the body. As a common malignant tumor of the head and neck, oral squamous cell carcinoma also relies on abnormally activated signaling networks and molecular interactions for its occurrence, invasion and metastasis. Accordingly, the specific expression patterns and functional mechanisms of scaffold proteins in OSCC have attracted increasing attention. The following part mainly reviews research progress of scaffold proteins in oral squamous cell carcinoma.

6. Research progress of scaffold proteins in oral squamous cell carcinoma

Paxillin (PXN) is a classic enzymatically inactive scaffold protein in the focal adhesion signaling network. It was first systematically identified and named in 1990. Paxillin is primarily localized to focal adhesions at the cell-matrix interface and does not participate in the assembly of cell-cell adhesive junctions [30]. A study published in 2021 found that the relative mRNA and protein expression levels of FAK and paxillin were markedly elevated in side population (SP) cells of the OSCC cell line SCC-55. Meanwhile, the level of matrix metalloproteinase-11 (MMP-11) was also significantly increased in SP cells. After silencing paxillin expression via RNA interference, SP cells became more sensitive to chemotherapeutic drugs. These results demonstrate that upregulated paxillin expression is closely associated with increased chemoresistance, accelerated proliferation, and enhanced migration and invasion potential of SP cells [31].

Apart from the fact that endogenous paxillin overexpression in tumor cells facilitates cell proliferation, invasion and chemoresistance, the malignant progression of OSCC is also subjected to elaborate regulation by the tumor microenvironment. Among relevant regulatory pathways, the mechanical signaling axis composed of carcinoma-associated fibroblasts (CAFs), extracellular matrix (ECM) and scaffold proteins acts as a core regulatory pathway linking microenvironment remodeling and malignant phenotypes of tumor cells, which further complements the regulatory network of paxillin and FAK in OSCC. A pivotal study in 2023 confirmed that OSCC-associated CAFs secrete small extracellular vesicles (sEVs) rich in active lysyl oxidase (LOX). These vesicles bind directly to type I collagen via surface integrin α2β1 and catalyze collagen cross-linking, thus triggering stiffening and remodeling of the ECM. The stiffened ECM serves as a mechanical signal to robustly activate the phosphorylation of FAK (pY397) and paxillin (pY118). The downstream YAP signaling is then activated to induce epithelial-mesenchymal transition (EMT) in tumor cells, and ultimately accelerate the invasion and metastasis of OSCC. This mechanism identifies the CAF–ECM–FAK/paxillin axis as the core signaling pathway whereby the tumor microenvironment regulates malignant progression of OSCC. It also extends the functions of scaffold proteins including paxillin from intracellular signal scaffolds to key hubs transmitting microenvironmental mechanical signals into cells [32].

Nevertheless, existing studies on scaffold proteins in OSCC still have obvious limitations. Most researches only conduct linear analysis on a single signaling pathway, while systematic exploration of cross-regulation among multiple pathways is lacking. Moreover, current studies fail to integrate mechanical signals from the tumor microenvironment and intracellular calcium signals into a unified analytical framework, making it difficult to fully clarify the complete regulatory mechanisms of

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scaffold proteins during tumor malignant progression. Among numerous scaffold proteins involved in the precise regulation of calcium signals, the HOMER protein family specifically binds key molecules in calcium signaling and modulates the functions of mechanosensitive calcium channels. Such core characteristics make HOMER an ideal candidate to fill the above research gaps [33].

7. Research progress of the HOMER protein family and HOMER3

In 1997, the Worley team published a pioneering study in Nature. They cloned and identified HOMER1, the first member of this protein family, from rat hippocampal neurons. HOMER1 was confirmed as a novel scaffold protein that specifically binds type 5 metabotropic glutamate receptor (mGluR5). Its encoding gene is an immediate early gene associated with neuronal excitation, laying a fundamental foundation for subsequent functional research on this family [34]. In 1998, two other core members of the family, HOMER2 and HOMER3, were discovered successively, formally establishing the three-member system of the mammalian HOMER family [35].

The HOMER family consists of evolutionarily highly conserved scaffold proteins that exist exclusively in animals. In mammals, the family includes three independently encoded members: HOMER1, HOMER2 and HOMER3. Each member can generate multiple isoforms through alternative splicing, which are generally classified into long isoforms and short isoforms by researchers [36]. Long isoforms are constitutively and stably expressed, containing a conserved N-terminal class II EVH1 domain and a C-terminal coiled-coil leucine zipper self-assembly domain. The EVH1 domain can specifically recognize the PPxxF motif of target proteins and bind key molecules throughout the calcium signaling cascade, such as IP_3R, RyR and TRPC calcium channels. Meanwhile, the C-terminal domain enables protein multimerization to form nanoscale calcium signaling microdomains, so as to achieve precise spatiotemporal regulation of signal transduction. In contrast, short isoforms are only found in Homer1. Lacking the C-terminal self-assembly domain, they act as products of neuronal activity-induced immediate early genes and exert endogenous dominant-negative regulatory effects [36]. Early studies mainly focused on the functions of the Homer family in synaptic plasticity of the central nervous system. Subsequent research has verified that these proteins are widely expressed in various non-neural peripheral tissues and participate in regulating core biological behaviors including cell proliferation, differentiation and migration. In particular, HOMER3 plays a vital role in the initiation and progression of tumors.

In most epithelial-derived solid tumors, HOMER3 acts as a definite oncogenic factor and serves as a core functional molecule driving malignant tumor progression. In muscle-invasive bladder cancer (MIBC), hypoxia and glucose deprivation within the tumor microenvironment induce the translocation of cytoplasmic HOMER3 to the cell membrane, forming tumor-specific glycosylated isoforms modified with short-chain O-glycans. This membrane-localized HOMER3 is highly expressed in MIBC tissues and distant metastatic lesions, and its positive expression rate rises gradually with the increase of tumor stage. It is an independent prognostic factor for poor overall survival of patients. Functionally, membrane-localized HOMER3 markedly enhances the proliferation and invasion abilities of bladder cancer cells as well as their adaptability to hypoxic microenvironments. Given its extremely low expression in normal tissues, HOMER3 is a promising candidate target for precise targeted therapy of bladder cancer [37]. In non-small cell lung cancer (NSCLC), HOMER3 is characteristically overexpressed, and its expression level shows a significant positive correlation with tumor diameter, multiple nodular lesions and serum gamma-glutamyl transferase (GGT) levels of patients. Mechanistically, HOMER3 collaborates with PAFAH1B3 to upregulate GABPB1, a key transcription factor for mitochondrial biogenesis. It modulates

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mitochondrial oxidative phosphorylation and aspartate biosynthesis, remodels the metabolic phenotype of tumor cells, and ultimately facilitates the proliferation, invasion and in vivo metastasis of NSCLC cells. Hence, HOMER3 represents a potential novel target for metabolic targeted intervention against NSCLC [38]. In triple-negative breast cancer (TNBC), HOMER3 functions as a core scaffold protein. It directly mediates growth factor-induced tyrosine phosphorylation and nuclear translocation of β-catenin, continuously activates the oncogenic Wnt/β-catenin signaling pathway, and greatly strengthens the proliferation, invasion and distant metastasis capacities of TNBC cells. It is a key driver for metastatic progression and a biomarker indicating poor prognosis in TNBC [39]. In hepatocellular carcinoma (HCC), the functions of HOMER3 present distinct context-dependent heterogeneity. On one hand, as a major downstream effector of lncRNA HOMER3-AS1, HOMER3 is significantly upregulated in HCC tissues. It drives malignant proliferation and invasion of tumor cells by activating the Wnt/β-catenin pathway, and acts as the principal functional mediator through which HOMER3-AS1 regulates HCC progression [40]. On the other hand, in hepatitis B virus-related HCC (HBV-HCC), HOMER3 is characteristically downregulated in cancer tissues and peripheral blood of patients. Its expression level is negatively correlated with tumor differentiation degree, tumor size and invasiveness. Combined with Homer2 and the traditional biomarker AFP, it can raise the area under the receiver operating characteristic curve (AUC) for HBV-HCC diagnosis to 0.900, suggesting that HOMER3 may exert potential tumor-suppressive effects in the development of HBV-associated liver cancer [41].

To sum up, HOMER3 exhibits highly diverse expression patterns and biological effects in malignant tumors, and its functions are strictly determined by tumor type, etiological background and characteristics of the tumor microenvironment. In the majority of solid tumors, HOMER3 is a crucial oncogenic molecule that drives tumor cell proliferation, invasion, metabolic reprogramming and remodeling of the immune microenvironment. It can not only serve as a new biomarker for prognostic stratification of tumor patients, but also provide novel research directions and intervention strategies for precision targeted therapy of malignant tumors due to its tumor-specific expression and localization features.

Nevertheless, research on the roles and mechanisms of HOMER3 in OSCC remains largely unexplored. An original study published in The Journal of Biological Chemistry in 2014 revealed a new mechanism in non-excitable salivary gland acinar cells. It demonstrated that HOMER2 specifically binds plasma membrane calcium ATPase (PMCA) and negatively regulates calcium efflux and cellular calcium homeostasis. This finding fills the research gap regarding the clearance process of calcium signaling modulated by the HOMER family. Meanwhile, it provides direct tissue homology evidence for exploring the functions of the HOMER family in oral epithelial cells (Table 3) [42].

Table 3. Reported biological functions of HOMER3 in different malignancies

Cancer Type	HOMER3 Expression Pattern	Major Mechanism	Biological Effects	Clinical Significance	Reference
Bladder cancer	Upregulated	Membrane translocation under hypoxia/glucose deprivation	Promotes proliferation, invasion, adaptation to hypoxia	Poor prognosis biomarker and therapeutic target	[37]

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Table 3. (continued)

Non-small cell lung cancer	Upregulated	Regulates GABPB1-mediated mitochondrial metabolism	Enhances proliferation and metastasis	Associated with aggressive clinicopathological features	[38]
Triple-negative breast cancer	Upregulated	Activates β-catenin signaling	Promotes metastasis and tumor progression	Potential metastatic driver	[39]
Hepatocellular carcinoma	Upregulated (HOMER3-AS1 axis)	Activates Wnt/β-catenin signaling	Promotes proliferation and invasion	Functional downstream effector of lncRNA HOMER3-AS1	[40]
HBV-related HCC	Downregulated	Mechanism unclear	Potential tumor suppressive role	Diagnostic biomarker with AFP and HOMER2	[41]
Salivary gland acinar cells	Functionally expressed	Regulates PMCA-mediated calcium extrusion	Maintains intracellular calcium homeostasis	Provides mechanistic basis for oral epithelial studies	[42]

8. Conclusions and perspectives

8.1. Conclusions

As the most prevalent epithelial malignant tumor of the head and neck, oral squamous cell carcinoma (OSCC) is confronted with clinical dilemmas including low early diagnosis rate and long-term stagnation of the five-year survival rate. The three classic carcinogenic factors, namely tobacco use, alcohol consumption and HPV infection, cannot fully explain its pathogenesis [7]. Chronic mechanical irritation (CMI), a unique physical stimulus to the oral mucosa, has been verified by epidemiological investigations, animal experiments and epigenetic studies to be closely associated with OSCC. CMI can directly induce precancerous lesions such as oral leukoplakia and synergistically enhance carcinogenic risks together with tobacco and alcohol [8, 9, 12]. It also triggers abnormal remodeling and increased stiffness of the extracellular matrix (ECM), forming a pro-tumor mechanical microenvironment. Hence, CMI acts as a critical bridge linking external physical stimulation to the malignant transformation of oral epithelial cells.

Mechanosensitive signal transduction induced by elevated ECM stiffness constitutes a core mechanism driving the malignant progression of OSCC. A cascade of signals, with Hippo-YAP/TAZ serving as the transcriptional hub, PIEZO1/TRPV4-mediated calcium influx as key nodes, and pathways such as MAPK as effector executors, converts extracellular mechanical stimuli into intracellular biochemical signals [16, 18]. The precise spatiotemporal regulation of this complex network relies heavily on scaffold proteins. Breaking away from the traditional definition as a passive assembly platform, scaffold proteins function as spatial placemakers and temporal pacemakers for signal transduction. They anchor core components of signaling pathways via modular domains, and determine the efficiency, specificity of signal transmission as well as cell fate [19]. Classic scaffold proteins represented by FAK and paxillin have been confirmed as vital hubs connecting the ECM mechanical microenvironment and malignant phenotypes of OSCC cells. They form the core mechanical signaling axis of CAF-ECM-scaffold protein-YAP, which facilitates tumor cell proliferation, invasion, chemoresistance and epithelial-mesenchymal transition [31, 32].

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Among various scaffold proteins, HOMER3 stands out as a promising candidate to fill the research gaps in OSCC owing to its specific regulatory capacity over the entire calcium signaling cascade. As an evolutionarily highly conserved scaffold protein, HOMER3 establishes functional microdomains for calcium signals through its EVH1 domain and realizes precise spatiotemporal regulation of calcium signaling [36]. Existing studies have demonstrated that HOMER3 exerts a definite oncogenic effect in most epithelial-derived solid tumors and is closely correlated with tumor progression and poor patient prognosis. In hepatocellular carcinoma, it presents dual functions dependent on etiological factors, reflecting tumor-specific regulatory characteristics [37-41]. Although the functional mechanisms of HOMER3 in OSCC remain largely unclarified, its family members have been proven to regulate calcium homeostasis in salivary gland acinar cells, providing important tissue homology evidence for exploring the functions of HOMER family in oral epithelial cells [42].

In summary, this paper systematically elaborates the complete regulatory cascade: CMI-induced ECM mechanical remodeling, mechanosensitive signal transduction, spatiotemporal regulation by scaffold proteins, and eventual malignant progression of OSCC. It clarifies the central regulatory role of scaffold proteins in the occurrence and development of OSCC. HOMER3, as a key scaffold protein integrating calcium signals and mechanical signals, represents a promising new direction for mechanistic research, biomarker development and targeted therapy of OSCC. This study establishes an integrated theoretical framework for basic research and clinical transformation of OSCC.

8.2. Perspectives

Current studies on scaffold proteins in OSCC are mostly limited to linear analysis of single pathways and single molecules, failing to form an integrated understanding of mechanical signals and calcium signals. The biological functions and clinical values of HOMER3 in OSCC still remain unexplored. Further research can be carried out focusing on the following key directions in the future.

First, systematically analyze the expression patterns and biological functions of HOMER3 in OSCC. Based on large-scale clinical cohorts, clarify the expression characteristics of HOMER3 in normal oral mucosa, precancerous lesions, primary tumors and metastatic lesions. Analyze its correlations with clinicopathological features and patient prognosis, and verify its potential as a prognostic biomarker for OSCC. Conduct in vivo and in vitro functional experiments to explore how HOMER3 regulates malignant phenotypes of OSCC cells including proliferation, invasion and drug resistance. In addition, establish animal models of carcinogenesis induced by CMI combined with other carcinogenic factors to define the core role of HOMER3 in epithelial malignant transformation triggered by chronic mechanical irritation.

Second, reveal the molecular mechanisms by which HOMER3 mediates the integrated regulation of mechanical signals and calcium signals in OSCC. Focus on verifying whether HOMER3 anchors mechanosensitive calcium channels such as PIEZO1 and TRPV4 as well as downstream effector molecules on the cell membrane through its scaffold function, so as to construct mechanosensitive calcium signaling microdomains, amplify calcium influx and activate downstream oncogenic pathways. Meanwhile, explore the interactions between HOMER3 and classic scaffold proteins such as FAK and paxillin, and build an integrated regulatory network of mechanical signals mediated by scaffold proteins in OSCC. This will fundamentally elucidate the molecular mechanism underlying tumor progression driven by the mechanical microenvironment.

Third, explore the translational application values and tissue-specific rules of scaffold proteins in the diagnosis and treatment of OSCC. In terms of diagnosis, detect the expression levels of

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HOMER3 and other scaffold proteins in patients' saliva and peripheral blood, and evaluate their feasibility as biomarkers for early non-invasive screening of OSCC and risk warning of malignant transformation of precancerous lesions. In terms of treatment, carry out research on targeted intervention of scaffold proteins, verify the inhibitory effect of targeted blockade of HOMER3 protein interaction on malignant phenotypes of OSCC, and explore combined strategies with chemotherapy and immunotherapy. Moreover, focus on the tissue specificity of oral mucosa, analyze the differences in expression and functions of scaffold proteins among different anatomical oral sites, and explain the high susceptibility to CMI-related carcinogenesis at sites such as the lateral tongue margin at the molecular level. The above findings will provide theoretical basis for precise prevention and treatment of OSCC.

In conclusion, research on scaffold proteins centered on HOMER3 will not only fill the mechanistic gaps in the integrated regulation of mechanical signals and calcium signals in OSCC, but also is expected to bring new breakthroughs for early diagnosis and targeted therapy of OSCC, and ultimately achieve the clinical goal of improving patient prognosis.

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