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Review

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Roles of Wnt ligands and receptors in oral squamous cell carcinoma

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Abstract: Oral squamous cell carcinoma (OSCC) poses significant challenges in terms of diagnosis and treatment, with high rates of morbidity and mortality. Emerging evidence highlights the critical involvement of Wingless/Int-1 (Wnt) ligands and receptors in OSCC pathogenesis. Dysregulated Wnt signaling pathways contribute to tumor initiation, progression, and therapy resistance by promoting cellular proliferation, epithelial–mesenchymal transition (EMT), and the maintenance of cancer stem cells (CSCs). Targeting Wnt signaling presents a promising therapeutic avenue, yet its complex interplay with other signaling pathways requires a deeper understanding to implement effective intervention. This study sheds light on the current knowledge of the roles of Wnt ligands and receptors in OSCC, emphasizing their potential as diagnostic biomarkers and therapeutic targets. Future research directions involve elucidating context-specific Wnt signaling dynamics and exploring combination therapies to improve clinical outcomes for OSCC patients.

Key words: Oral squamous cell carcinoma (OSCC); Wingless/Int-1 (Wnt) signaling; Molecular mechanism; Tumorigenesis; Therapeutic target

1 Introduction

The Wingless/Int-1 (Wnt) signaling pathway is crucial in oral cancer development, affecting cell survival, migration, polarity, and proliferation. Oral cancer cells express *Wnt* genes, notably *Wnt5a* and frizzled-5 (*Fzd5*), stimulating migration and invasion. Dysregulated Wnt components like *Wnt5a* can be markers for oral carcinogenesis. The activated Wnt pathway highlights the need for therapeutic targets and prognostic markers in oral cancer transformation. The Wnt signaling pathway is crucial in cancer, governing proliferation, differentiation, apoptosis, and migration. It is involved in tumor initiation, growth, senescence, differentiation, and metastasis. Research has focused on Wnt as a cancer treatment target, with clinical trials testing small molecules like LGK974 and biological agents like OMP-18R5. A deeper understanding of gene functions has advanced targeted tumor therapies (Zhang et al., 2020).

Understanding the roles of Wnt ligands and receptors in oral squamous cell carcinoma (OSCC) requires a comprehensive exploration of their functions and interactions within the complex tumor microenvironment (TME). The ligands, which comprise Wnt family members like Wnt1, Wnt3a, and Wnt5a, function as signaling molecules that bind to receptors on the cell surface, initiating signaling cascades downstream. The receptors involved in Wnt signaling, including FZD receptors and co-receptors such as low-density lipoprotein receptor-related protein 5/6 (LRP5/6), mediate the transduction of Wnt signals into the cell, regulating gene expression and cellular behavior (Noguti et al., 2012, Reyes et al., 2020).

In OSCC, abnormal levels of Wnt ligands and receptors play a significant role in different stages of cancer development, such as tumor formation, epithelial–mesenchymal transition (EMT) (Krisanaprakornkit and Iamaroon, 2012; Bai et al., 2020), angiogenesis (Farrapo

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et al., 2022), and metastasis (Tan et al., 2023). In addition, the interaction between Wnt signaling and other cancer-causing pathways adds complexity to our comprehension of how OSCC progresses. For example, Wnt signaling can enhance the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway through β-catenin stabilization, promoting cell survival, while AKT activation, in turn, can increase β-catenin activity. Additionally, Wnt signaling can modulate phosphatase and tensin homolog (PTEN), influencing PI3K/AKT pathway regulation (Yu et al., 2021; He and Gan, 2023). This phenomenon is well-known in other cancers, such as colorectal cancer (Prossomariti et al., 2020; Fleming-de-Moraes et al., 2022), but studies related to OSCC are lacking.

This review aims to provide a comprehensive overview of the roles played by Wnt ligands and receptors in OSCC, synthesizing the existing literature to elucidate their multifaceted functions and underlying mechanisms. By examining the impact of Wnt signaling dysregulation on OSCC pathogenesis, we aim to identify potential therapeutic targets and strategies for the management of this devastating disease. By enhancing our understanding of Wnt signaling in OSCC, we endeavor to make a valuable contribution to the advancement of innovative therapeutic interventions, ultimately leading to improved patient outcomes and quality of life.

2 Wnt ligands in OSCC

2.1 Canonical Wnt ligands in OSCC

2.1.1 Wnt1

Canonical Wnt ligands are crucial regulators of various cellular processes, including proliferation, differentiation, and migration, and they play significant roles in the progression of OSCC (Table 1). Wnt1 plays an important role in OSCC tumorigenesis, having

Table 1 Roles of canonical Wnt ligands in OSCC progression

Wnt ligand	Role in OSCC	Mechanism of action
Wnt1	Elevated expression in OSCC tissues, indicating significant involvement in OSCC progression	Canonical Wnt pathway activation via FZD and LRP5/6 co-receptors β-Catenin stabilization and nuclear translocation, activating genes for cell cycle progression and survival
Wnt3a	Heightened expression in OSCC tissues, particularly in advanced stages. Implicated as a key driver of OSCC pathogenesis	Canonical Wnt signaling activation via FZD and LRP5/6 co-receptors β-Catenin stabilization and nuclear translocation Complex formation with TCF/LEF, activating genes for proliferation, survival, and EMT Promotion of EMT in OSCC, enhancing invasiveness and metastasis
Wnt8a	Vital function in regulating diverse cellular activities, including self-renewal, proliferation, differentiation, and motility Specific role in OSCC progression yet to be fully elucidated	Plausible impact on OSCC pathogenesis through the canonical Wnt signaling pathway, similar to other Wnt family members
Wnt8b	Identified as an independent prognostic marker for nasopharyngeal carcinoma Role in OSCC progression not extensively documented	Promotion of cell proliferation and migration through activation of cyclin D1 and c-Myc expression, suggesting potential implications for OSCC malignancy
Wnt10a	Implicated in the progression of OSCC	Regulations of proliferation, stemness, pluripotency, and cell fate via Wnt/β-catenin signaling Upregulated in late-stage OSCC, indicating a role in tumor progression
Wnt10b	Significantly involved in OSCC progression	Regulation of bone metabolism by controlling osteoblast differentiation and interacting with Wnt signaling transcription factors A suppressor of adipocyte differentiation, potentially affecting the osteoblast–adipocyte balance in the OSCC tumor microenvironment

Wnt: Wingless/Int-1; OSCC: oral squamous cell carcinoma; FZD: frizzled; LRP5/6: lipoprotein receptor-related protein 5/6; TCF/LEF: T-cell factor/lymphoid enhancer factor; EMT: epithelial–mesenchymal transition; c-Myc: cellular-myelocytomatosis viral oncogene.

elevated expression levels in OSCC tissues compared to normal oral mucosa, indicating its crucial involvement in OSCC progression (Cierpikowski et al., 2023). Mechanistically, Wnt1 activates the canonical Wnt pathway by interacting with FZD receptors and LRP5/6 co-receptors, leading to the stabilization of β-catenin and its translocation into the nucleus. This nuclear translocation of β-catenin enables its binding to transcription factors like T-cell factor/lymphoid enhancer factor (TCF/LEF), thereby initiating the transcription of target genes essential for cell cycle progression and proliferation (Cadigan and Waterman, 2012; Xie et al., 2021). One of the key target genes activated by Wnt1 signaling is cyclin D1, a critical regulator of cell cycle progression from G_1 to S phases, promoting uncontrolled cell proliferation and tumor growth in OSCC. In addition, the activation of the canonical Wnt pathway by Wnt1 results in the elevation of cellular-myelocytomatosis viral oncogene (c-Myc), a transcription factor recognized for its role in promoting cell proliferation and survival (Zhang et al., 2014; Ma et al., 2017). The concurrent influence of cyclin D1 and c-Myc emphasizes the capacity of Wnt1 to facilitate the proliferation and advancement of OSCC tumors by promoting cell cycle progression and survival.

WISP1, part of the Wnt1-inducible signaling pathway proteins, plays a role in cell proliferation, differentiation, and wound healing. A study found elevated WISP1 levels in OSCC tissues, which were linked to treatment failure and lower 5-year survival rates (Jung et al., 2017). Experiments confirmed that WISP1 promotes invasive behavior and inhibits apoptosis in OSCC cells. These findings highlight WISP1 as a potential therapeutic target for combating aggressive behavior in oral cancer. A study on WISP1, which is linked to carcinogenesis, examined *WISP1* single nucleotide polymorphisms (SNPs) in 900 OSCC patients and 1200 cancer-free individuals (Lau et al., 2017). Carriers of the *WISP1* rs2929970 polymorphism, especially with a G allele, were more susceptible to OSCC. Non-smokers with specific *WISP1* variants had late-stage, larger tumors, while betel quid chewers with certain variants had a lower risk of lymph node metastasis. These findings suggest that *WISP1* polymorphisms, along with smoking and betel nut chewing, influence OSCC risk and could be useful for marker identification and therapeutic targeting.

A recent study investigated the prognostic significance of WNT1, neurogenic locus notch homolog protein 1 (NOTCH1), platelet-derived growth factor receptor β (PDGFRβ), and CXC subfamily receptor 4 (CXCR4) in OSCC (Cierpikowski et al., 2023). Immunohistochemistry of 60 OSCC samples revealed the presence of WNT1, NOTCH1, PDGFRβ, and CXCR4 in 51.7%, 25.0%, 63.3%, and 70.0% of patients, respectively. WNT1 correlated with NOTCH1 and CXCR4, and NOTCH1 correlated with CXCR4. WNT1 and PDGFRβ expression levels were linked to decreased overall survival. Multivariate analysis identified WNT1 and CXCR4 as independent prognostic factors. The study suggested that WNT and NOTCH signaling pathways contribute to OSCC angiogenesis, with WNT1 and CXCR4 as potential prognostic indicators.

Quercetin, a compound with potential benefits in various carcinomas, including OSCC, affects the Wnt/β-catenin pathway and microRNA (miRNA) regulation. Research has assessed its impact on miR-22 and the Wnt1/β-catenin pathway in OSCC (Zhang et al., 2019). Cell counting kit-8 (CCK-8) and flow cytometry analyses showed that quercetin and miR-22 overexpression decreased cell viability and increased apoptosis in OSCC. Wnt1 was identified as a direct target of miR-22 through bioinformatics and luciferase assays. Quercetin enhanced miR-22 expression and inhibited Wnt1 and β-catenin in OSCC cells, but this effect was negated when miR-22 was inhibited. In vivo studies confirmed that quercetin inhibited OSCC tumor growth by upregulating miR-22 and suppressing the Wnt1/β-catenin pathway. These findings highlight potential of quercetin as a therapeutic agent in OSCC treatment.

2.1.2 Wnt3a

Wnt3a has emerged as a pivotal player in the progression of OSCC, as evidenced by its heightened expression levels in OSCC tissues, particularly in the advanced stages of the disease (Purwaningsih et al., 2021). This elevated expression of Wnt3a implicates it as a key driver of OSCC pathogenesis.

Mechanistically, Wnt3a exerts its effects by activating the canonical Wnt signaling pathway (Reyes et al., 2020; Purwaningsih et al., 2021). Wnt3a binds to FZD receptors and LRP5/6 co-receptors to initiate the canonical Wnt pathway, stabilizing β-catenin and allowing it to move into the nucleus, where it complexes with TCF/LEF transcription factors. This complex activates genes related to cell proliferation, survival, and EMT. The activation of these genes by Wnt3a enhances

OSCC cell survival, helping them evade apoptosis and persist in the TME (Reyes et al., 2020).

Furthermore, Wnt3a-mediated signaling contributes to the induction of EMT in OSCC cells. This process gives cancer cells invasive and migratory properties, enabling them to disseminate from the primary tumor site and invade surrounding tissues, ultimately facilitating metastasis (Reyes et al., 2020; Purwaningsih et al., 2021). Therefore, Wnt3a's activation of the canonical Wnt signaling pathway plays a crucial role in the progression of OSCC, facilitating tumor growth, survival, and metastasis (Shiah et al., 2015; Xie et al., 2021). For example, a recent study found that cyclin-dependent kinase 5 regulatory subunit-associated protein 2 (CDK5RAP2) expression is elevated in OSCC and regulated by the Wnt signaling pathway (Shen et al., 2023). Downregulating CDK5RAP2 disrupts spindle orientation, significantly impeding OSCC progression and altering the cancer stem cell (CSC) signature of OSCC. These findings highlight the role of CDK5RAP2 in OSCC progression and its potential as a CSC marker and therapeutic target. Understanding the intricate mechanisms underlying Wnt3a-mediated signaling provides valuable insights into potential therapeutic targets for OSCC treatment, offering avenues for the development of targeted therapies aimed at mitigating OSCC progression and improving patient outcomes.

2.1.3 Wnt8a and Wnt8b

Wnt8a, as a constituent of the Wnt family, assumes a vital function in regulating diverse cellular activities, encompassing self-renewal, proliferation, differentiation, and motility (Ngernsombat et al., 2021). The specific role of Wnt8a in OSCC remains to be fully elucidated. However, given the established functions of Wnt family members in promoting or suppressing tumor progression via the canonical Wnt signaling pathway, it is plausible that Wnt8a may similarly impact OSCC pathogenesis.

Wnt8b, another member of the Wnt family, has been identified as an independent prognostic marker for nasopharyngeal carcinoma (Ngernsombat et al., 2021). While the direct involvement of Wnt8b in OSCC progression is not extensively documented in the literature, its role in other cancers suggests potential implications for OSCC (Nie et al., 2020; Ngernsombat et al., 2021). Research has shown that Wnt8b can promote cell proliferation and migration through the activation of cyclin D1 and c-Myc expression (Ma et al., 2017). This mechanism may enhance OSCC malignancy by regulating cell cycle progression and invasion. While the specific roles of Wnt8a and Wnt8b in OSCC are not well-detailed, their known functions in cell regulation suggest that they could significantly influence OSCC pathogenesis, affecting cell proliferation, migration, and other cancer-related pathways. Further research on these Wnt proteins in OSCC could reveal their precise contributions to tumor growth and metastasis.

2.1.4 Wnt10a and Wnt10b

Wnt10a is implicated in OSCC progression and plays crucial roles in various tissues, including bone, adipocytes, teeth, skin, hair, immune system, muscle, placenta, and heart. Abnormal Wnt10a signaling is linked to diseases like cancer, obesity, and osteoporosis. In OSCC, Wnt10a significantly regulates proliferation, stemness, pluripotency, and cellular fate by activating the Wnt/β-catenin signaling pathway (Ma et al., 2017). Furthermore, the high levels of Wnt10a expression observed in the advanced stages of OSCC indicate its potential role in tumor progression. The upregulation of Wnt10a in late-stage OSCC suggests its involvement in promoting tumorigenesis and disease advancement (Kalinke et al., 2016).

Wnt10b, a member of the Wnt family, activates the canonical Wnt/β-catenin signaling pathway to regulate various cellular functions in different tissues. It is crucial for osteoblast differentiation and the induction of osteoblast genes. In OSCC, Wnt10b plays a significant role in influencing cell proliferation, differentiation, and potentially metastasis. Wnt10b suppresses adipocyte differentiation, indicating enhanced osteoblastogenesis and reduced adipogenesis, which may impact the balance between osteoblasts and adipocytes in the OSCC TME. Dysregulation of Wnt10b affects OSCC progression. Additionally, a study found that restoring miR-148a levels in cancer-associated fibroblasts (CAFs) impaired OSCC cell migration and invasion by targeting Wnt10b (Min et al., 2016).

Overall, both Wnt10a and Wnt10b significantly contribute to OSCC progression by impacting crucial cellular processes related to tumor growth and metastasis. Their roles in regulating tissue-specific functions and disease states highlight their potential as therapeutic targets for OSCC management. Investigating the

precise mechanisms by which these Wnt proteins influence OSCC pathogenesis could offer valuable insights for developing targeted treatment strategies.

2.2 Non-canonical Wnt ligands

The non-canonical Wnt pathway, unlike the canonical Wnt/β-catenin pathway, does not stabilize β-catenin or activate its associated transcriptional programs. Instead, it primarily regulates cell movement and polarity through pathways such as planar cell polarity (PCP) and Wnt/Ca^{2+} signaling, which are crucial for processes like migration and cytoskeletal rearrangement—key factors in cancer progression. In OSCC, non-canonical Wnt ligands such as Wnt5a/b and Wnt7a/b play significant roles in tumor progression. Wnt5a is frequently upregulated in OSCC and is linked to increased cell migration and invasion (Prgomet et al., 2017), possibly through the activation of the Rho and Rac signaling pathways, which are essential for cytoskeletal dynamics and motility (Bueno et al., 2022). Similarly, Wnt7a/b has been associated with modulation of the TME, promoting cancer cell proliferation and invasion by activating downstream effectors like c-Jun N-terminal kinase (JNK) and Ca^{2+}/nuclear factor of activated T (NFAT) cells contributing to a more aggressive tumor phenotype. These non-canonical pathways result in distinct cellular outcomes compared to the canonical Wnt pathway, which primarily drives cell proliferation through β-catenin signaling. Understanding these differences is vital for elucidating the metastasis and tumor progression mechanisms in OSCC and underscores the potential for targeted therapies that could specifically disrupt the non-canonical Wnt signaling pathways involved in cancer progression.

2.2.1 Wnt5a and Wnt5b

Non-canonical Wnt ligands such as Wnt5a, Wnt5b, Wnt7a, and Wnt7b contribute to OSCC progression by promoting cell proliferation, migration, invasion, and metastasis (Table 2). Wnt5a is described as the "most important Wnt protein activating the non-canonical Wnt pathway" in OSCC (Prgomet et al., 2013). Research has shown that Wnt5a can regulate various cellular processes that are crucial for cancer progression, including proliferation, differentiation, migration, adhesion, and polarity (Prgomet et al., 2013). It has been specifically reported through various studies that Wnt5a can enhance the migration and invasion of

Table 2 Roles of non-canonical Wnt ligands in OSCC progression

Wnt ligand	Role in OSCC	Mechanism of action
Wnt5a	Activation of non-canonical Wnt signaling pathways, promoting migration, invasion, and potentially other cancer-related cellular processes in OSCC Correlation with poor prognosis and aggressive behavior in OSCC patients	Activation of Wnt/Ca^{2+}/PKC pathway, boosting OSCC cell migration and invasion Linked to OSCC invasiveness and histological grade Downregulated by ΔNp63β overexpression, increasing cell aggressiveness and MMP-2 production
Wnt5b	Promotion of migration and invasion of OSCC cells, contributing to metastatic behavior	Increased mRNA expression in highly metastatic OSCC cells Suppression of Wnt5b reduces migratory capacity; its application enhances migration and promotes filopodia-like protrusions in OSCC cells
Wnt7a	Notable upregulation in OSCC tissues compared to adjacent normal tissues Correlation with increased tumor growth, lymph node metastasis, advanced tumor staging, and shorter recurrence-free survival time Involvement in promoting EMT process, enhancing OSCC cell migration and invasion	Interactions with various signaling pathways including EGF/PI3K/AKT/Wnt7a/β-catenin/MMP-9 pathway Sensitization of OSCC cells to cisplatin treatment, enhancing apoptotic responses Stimulation of OSCC cells by CAFs to produce Wnt7a, contributing to tumor progression
Wnt7b	Gradual upregulation in OSCC tissues, suggesting involvement in tumor development and advancement Implicated in the promotion of tumor invasion and impacting resistance to anticancer therapies	Activation of canonical Wnt signaling pathways, regulating downstream genes like *MMP-1*, thereby augmenting the invasive capabilities of cancer cell

Wnt: Wingless/Int-1; OSCC: oral squamous cell carcinoma; PKC: protein kinase C; mRNA: messenger RNA; EGF: epidermal growth factor; PI3K/AKT: phosphoinositide 3-kinase/protein kinase B; MMP: matrix metalloproteinase; EMT: epithelial–mesenchymal transition; CAFs: cancer-associated fibroblasts.

OSCC cells by activating non-canonical Wnt signaling pathways, including the Wnt/Ca^{2+}/protein kinase C (PKC) pathway. A recent article states that Wnt5a activates this pathway, which promotes migration and invasion in OSCC (Xie et al., 2021). Additionally, the overexpression of Wnt5a is correlated with an unfavorable prognosis and aggressive demeanor in patients with OSCC. It is proposed that increased expression of Wnt5a protein in OSCC is correlated with an unfavorable clinical prognosis (Prgomet et al., 2017). According to a recent study, sex determining region Y-box 2 (SOX2) and octamer-binding transcription factor 4 (OCT4) indicate proliferative potential, while Wnt5a signifies invasiveness. Immunohistochemistry on 20 carcinoma, 20 dysplasia, and 25 normal tissue specimens revealed higher SOX2 levels in carcinoma, minimal OCT4 expression across samples, and increasing Wnt5a expression from normal to dysplastic and further to carcinoma tissues. SOX2 alone may serve as a proliferation marker, while Wnt5a may indicate OSCC invasiveness (Vijayakumar et al., 2020). Furthermore, a study used immunohistochemistry to examine Wnt5a and β-catenin expression levels in OSCC tissues. Most cases showed widespread cytoplasmic expression of both proteins. Statistical analysis revealed a positive correlation between Wnt5a expression and OSCC differentiation, while cytoplasmic β-catenin expression was inversely correlated with differentiation. Cytoplasmic β-catenin accumulation was associated with lymph node metastasis and loss of β-catenin on the cell membrane was inversely correlated with differentiation. These findings underscore the involvement of the Wnt/β-catenin pathway in OSCC tumorigenesis, metastasis, and prognosis, and Wnt5a is also linked to histological grade (Zhu et al., 2005). Another study investigated the influence of ΔNp63β, a variant associated with EMT, on cell motility in tongue squamous cell carcinoma (TSCC). DNA microarray analysis reveals that Wnt5a is significantly downregulated upon ΔNp63β overexpression in TSCC cells displaying an EMT phenotype. Wnt5a-Ror2 signaling was implicated in enhancing TSCC cell aggressiveness and promoting matrix metalloproteinase-2 (MMP-2) production, highlighting potential therapeutic targets for oral cancer treatment (Sakamoto et al., 2017). These studies show that Wnt5a plays a crucial role in OSCC progression by activating non-canonical Wnt signaling pathways, promoting cell migration, invasion, and other cancer-related processes. Overexpression of Wnt5a is associated with poor prognosis and aggressive behavior in OSCC patients, suggesting it as a potential therapeutic target for this cancer type.

Wnt5b, closely related to Wnt5a, shares 80.5% total amino acid identity. Recent studies reveal its significant role in promoting the migration and invasion of OSCC cells. Increased *Wnt5b* mRNA levels were observed in highly metastatic OSCC cell lines compared to less metastatic ones. Suppression of Wnt5b expression led to decreased migratory capacity, while its application enhanced migration. Wnt5b also facilitates the development of filopodia-like protrusions in OSCC cells, which are associated with increased motility and invasion (Takeshita et al., 2014). This observation underscores the role of Wnt5b in controlling cytoskeletal dynamics and cell motility, essential for OSCC metastasis. *Wnt5b* is pivotal in OSCC advancement, enhancing migration and invasion, likely by activating non-canonical Wnt signaling pathways and regulating cytoskeletal dynamics. These findings emphasize the significance of Wnt5b in OSCC metastatic behavior.

2.2.2 Wnt7a and Wnt7b

The emergence of Wnt7a as a key player in OSCC progression highlights its pivotal role in the cancer's aggressiveness. Comprehensive analysis reveals significant upregulation of Wnt7a in OSCC tissues at both mRNA and protein levels. This overexpression correlates with various critical aspects of OSCC advancement, including increased tumor growth, lymph node metastasis, and advanced tumor staging, indicating a poorer prognosis for patients. Elevated Wnt7a levels also correlate with shorter recurrence-free survival time. Additionally, the involvement of Wnt7a in promoting the EMT process elucidates its role in enhancing OSCC cell migration and invasion, crucial steps in metastasis (Jia et al., 2019). For example, analysis of Wnt7a mRNA and protein levels in TSCC tissues showed a notable increase compared to adjacent non-cancerous tissues. Clinical data analysis revealed a correlation between Wnt7a expression and T classification, lymph node metastasis, and pathological differentiation, suggesting a likelihood of shorter recurrence-free survival in TSCC patients. Suppressing Wnt7a expression inhibited cell proliferation, migration, and invasion, and reversed EMT in TSCC cell lines. These results suggest Wnt7a as an oncogene

and a potential therapeutic target in managing TSCC (Jia et al., 2019).

Recent studies highlight the multifaceted role of Wnt7a in OSCC progression, demonstrating its complex interaction with various signaling pathways. For instance, the interaction of Wnt7a with other signaling cascades significantly contributes to its oncogenic potential in OSCC. A recent study demonstrates that epidermal growth factor (EGF) stimulation increases Wnt7a mRNA and protein levels in OSCC cells, with phosphorylated AKT (p-AKT) mediating this induction. Inhibiting AKT activation prevents the upregulation of Wnt7a and MMP-9 expression caused by EGF, along with the translocation of β-catenin from the cytoplasm to the nucleus. Histological examination of OSCC specimens shows a significant association between Wnt7a expression and unfavorable clinical prognosis. These findings reveal a novel signaling pathway, PI3K/AKT/Wnt7a/β-catenin/MMP-9, implicated in the EGF-induced migration of OSCC cells (Xie et al., 2020). In a study involving 42 OSCC patients, *Wnt7a* mRNA was notably upregulated. Subsequent experiments on OSCC cell line KB cells showed that *Wnt7a* knockdown increased sensitivity to cisplatin treatment, with reduced nuclear β-catenin levels and increased cleaved caspase-3 and cleaved poly(ADP-ribose) polymerase (PARP) expression (Tian et al., 2018). In an in vivo mouse model, *Wnt7a* knockdown reduced tumor weight and volume, alongside increased apoptotic cell counts after cisplatin treatment. These findings suggest that inhibiting Wnt7a/β-catenin signaling could enhance cisplatin sensitivity in OSCC, providing insights for molecular diagnostics and treatment strategies (Tian et al., 2018).

The TME comprises cellular and non-cellular components that profoundly influence OSCC progression. Cancer cells interact with stromal cells, immune cells, extracellular matrix components, and signaling molecules within the TME, shaping tumor behavior and therapeutic responses. Stromal cells like CAFs, endothelial cells, and immune cells contribute to tumor growth, invasion, metastasis, angiogenesis, and immune evasion. For instance, a recent study investigated CAFs' impact on OSCC progression by exploring Wnt signaling activation. It found that CAFs stimulate OSCC cells to produce Wnt7a, enhancing tumor cell migration and invasion (Kayamori et al., 2023). High Wnt7a expression correlated with poor prognosis and downregulation of claudin 1 (*CLDN1*), a tumor suppression gene. Additionally, Wnt7a activation of AKT signaling contributed to *CLDN1* downregulation. These findings highlight the importance of targeting the TME in OSCC therapy (Kayamori et al., 2023). Hence, these findings solidify Wnt7a as a central orchestrator of OSCC aggressiveness, shedding light on its potential as a therapeutic target and prognostic marker in managing this challenging malignancy.

Emerging evidence of the role of Wnt7b in cancer progression underscores its significance in tumor development and resistance to anticancer therapies. Positioned within the intermediately transforming or non-transforming members of the Wnt family, the association of Wnt7b with cancer development and resistance mechanisms is increasingly evident (Kumar et al., 2021). Recent investigations have revealed a gradual upregulation of Wnt7b in oral lichen planus (OLP) and OSCC tissues, suggesting its potential involvement in oral inflammation and cancer progression. Notably, its heightened expression in OSCC tissues compared to adjacent normal tissues suggests a pivotal role in tumor development and advancement. Mechanistically, Wnt7b has been implicated in promoting tumor invasion by regulating downstream genes like *MMP-1*, thereby augmenting cancer cells' invasive capabilities. This facilitation of invasion is attributed to the activation of Wnt7b in canonical Wnt signaling pathways, which regulate key genes associated with cancer progression (Chen et al., 2022). In summary, Wnt7b has emerged as a critical player in OSCC, influencing tumor invasion and potentially impacting resistance to anticancer therapies. Its upregulation in OSCC tissues and its link to oral inflammation underscore its significance in the pathogenesis and progression of this cancer type. Further elucidation of the precise mechanisms by which Wnt7b modulates OSCC development and therapy resistance holds promise for the development of targeted therapeutic interventions.

Additionally, it is imperative to underscore the significance of other non-canonical Wnt ligands, including Wnt4, Wnt6, Wnt9a, Wnt9b, Wnt11, and Wnt16, in driving the progression of OSCC. Understanding the intricate interplay of these non-canonical Wnt ligands is crucial for unraveling the complex molecular landscape of OSCC and identifying novel therapeutic targets for more effective management of this aggressive malignancy.

3 Wnt receptors in OSCC

3.1 Frizzled receptors in OSCC

The Wnt signaling pathway, implicated in a range of cellular processes like cell proliferation, differentiation, and migration, relies heavily on the FZD receptors. These receptors consist of a family of ten transmembrane receptors. The development and progression of OSCC and other cancer types have been linked to the activity of these receptors (Zeng et al., 2018; Smith et al., 2021). The FZD receptors, which belong to the G-protein-coupled receptor (GPCR) family, are distinguished by the presence of a cysteine-rich domain (CRD) in their extracellular N-terminus. This CRD plays a crucial role in the binding of Wnt ligands. Upon the binding of Wnt ligands to the CRD of FZD receptors, downstream signaling cascades are activated, consisting of the canonical Wnt/β-catenin pathway and the non-canonical Wnt/PCP and Wnt/Ca^{2+} pathways (Zeng et al., 2018; Smith et al., 2021).

A number of studies have reported the dysregulation of FZD receptors in OSCC, suggesting their involvement in the pathogenesis of this disease (Umar et al., 2022). For example, FZD8 has been shown to be upregulated in head and neck carcinoma, and its overexpression is associated with increased expression of CSC markers and the activation of the extracellular signal-regulated kinase (ERK)/c-Fos signaling axis, leading to increased CSC activity and chemotherapeutic resistance (Sompel et al., 2021). Similarly, FZD7 is overexpressed in OSCC and is linked to EMT for cancer spread. A study on the impact of miR-27b on cisplatin sensitivity in OSCC found lower expression in drug-resistant tissues (Liu et al., 2019). Overexpressing miR-27b inhibited proliferation and migration, and boosted apoptosis in drug-resistant OSCC cells by suppressing FZD7/β-catenin signaling. In another investigation, miR-27b plays a crucial role in regulating OSCC cell proliferation by targeting FZD7 and the Wnt signaling pathway (Liu et al., 2017). Reduced miR-27b levels in OSCC cell lines were observed compared to those in controls. Overexpressing miR-27b notably hindered OSCC cell proliferation, suggesting its potential as a therapeutic target to disrupt key signaling pathways in cancer progression.

Given the important role of FZD receptors in the pathogenesis of OSCC, they have emerged as potential therapeutic targets (Fig. 1). Several small-molecule inhibitors and monoclonal antibodies targeting FZD receptors, such as G007-LK, G244-LM, and OMP-18R5, are currently under investigation for the treatment of OSCC and other cancers (Zeng et al., 2018; Umar et al., 2022). Furthermore, studies are currently investigating the efficacy of ICG-001, an inhibitor of the Wnt/β-catenin pathway that specifically targets the interaction between β-catenin and the transcriptional coactivator cAMP-response element-binding protein (CREB)-binding protein (CREBBP), for the treatment of OSCC (Kartha et al., 2018). Overall, FZD receptors play a crucial role in the pathogenesis of OSCC, and targeting these receptors or their associated signaling pathways holds promise as a potential therapeutic strategy for this disease.

3.2 LRP5 and LRP6

The LRP5 and LRP6 co-receptors are essential components of the canonical Wnt/β-catenin signaling pathway, which are widely recognized for their significant involvement in the development and progression of diverse cancer types (Roslan et al., 2019). LRP5 shows significant expression in the liver, pancreas, prostate, placenta, and small intestine, with lower levels in the ovary, thymus, skeletal muscle, colon, spleen, kidney, testis, heart, and lung. In contrast, LRP6 is highly expressed in the ovary, heart, brain, placenta, lung, kidney, pancreas, and spleen, while having lower levels in the liver, skeletal muscle, prostate, colon, and peripheral blood leukocytes. Despite distinct tissue expression, LRP5 and LRP6 share 71% amino acid sequence identity, indicating structural similarity (Joiner et al., 2013; Wang et al., 2018).

Both LRP5 and LRP6 contain an extracellular domain with YWTD-type β-propeller domains, EGF-like domains, and LDLR type A domains, as well as an intracellular domain with PPPSP motifs that are essential for Wnt signaling. These structural features allow them to function as co-receptors, binding to Wnt ligands and facilitating the activation of the canonical Wnt/β-catenin pathway (Wang et al., 2018; Ren et al., 2021). For example, in OSCC, fatatypical cadherin 1 (FAT1) expression changes significantly, impacting patient prognosis. Activated LRP5 signalosome links to poor outcomes. Loss of FAT1 function inhibits cell growth and metastasis in OSCC. Inhibiting FAT1 enhances cisplatin sensitivity in resistant OSCC cells by disrupting the LRP5/Wnt2/glutathione synthetase (GSS)

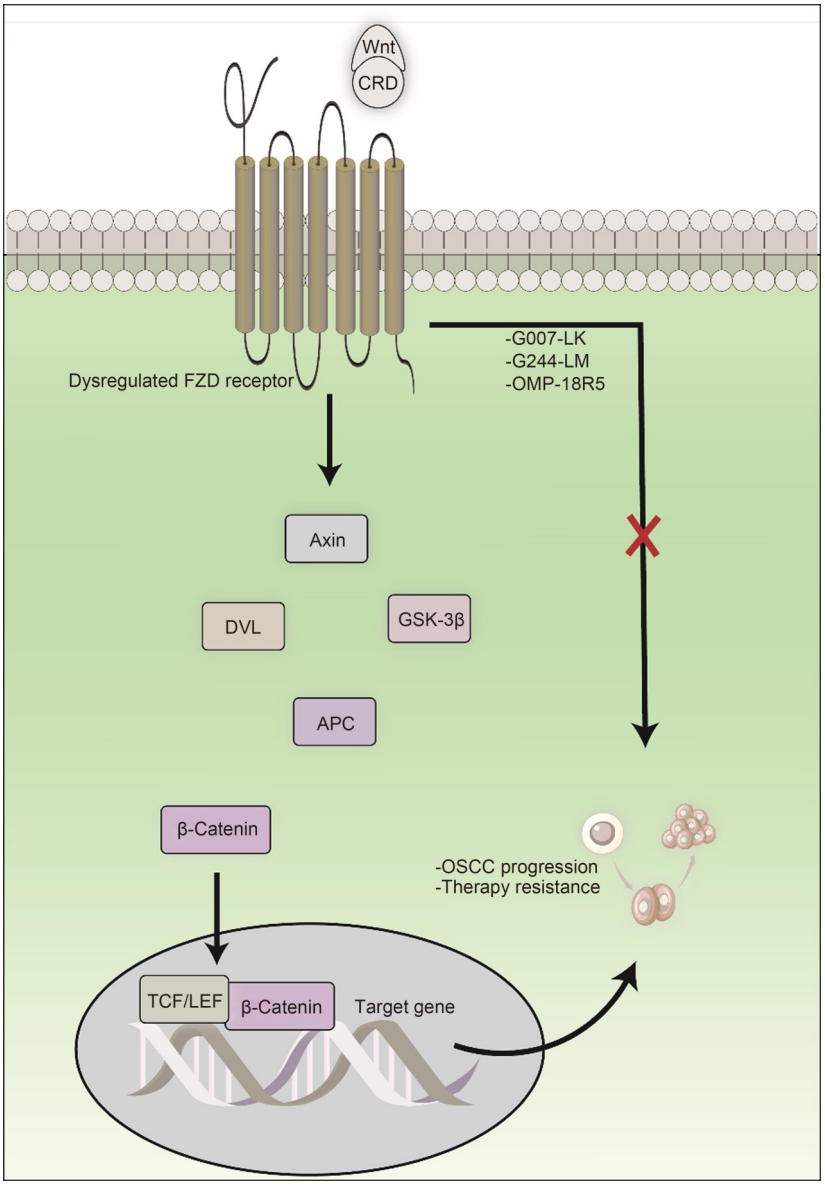

Fig. 1 Comprehensive explanation of key components illustrating the role frizzled (FZD) receptors play in oral squamous cell carcinoma (OSCC). It begins by showing FZD receptors, highlighting the cysteine-rich domain (CRD) crucial for binding Wnt ligands. The binding of Wnt ligands to the CRD is responsible for the initiation of downstream signaling cascades. Dysregulation of FZD receptors in OSCC is emphasized, along with the implications for OSCC progression, such as enhanced cancer cell strength and treatment resistance. Wnt: Wingless/Int-1; DVL: disheveled; GSK-3β: glycogen synthase kinase-3β; APC: adenomatous polyposis coli; TCF/LEF: T-cell factor/lymphoid enhancing factor.

pathway. FAT1 shows promise as a therapeutic target to enhance the effectiveness of cisplatin treatment in OSCC patients (Hsu et al., 2019). In another study, researchers used matrix-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS) proteomics to study OSCC development, revealing LRP6 upregulation in OSCC tissues linked to clinicopathologic factors. Inhibiting LRP6 suppressed OSCC cell growth. A positive correlation was found between LRP6 expression and the oncogene fibroblast growth factor 8 (*FGF8*) in OSCC cells (Yuan et al., 2017).

The involvement of LRP5 and LRP6 in the Wnt pathway suggests a key role in OSCC development and progression. Dysregulation of Wnt signaling is common in OSCC, with LRP5 and LRP6 potentially influencing tumor initiation, growth, and spread. Further research is essential to uncover their precise contributions and potential as therapeutic targets or biomarkers

in OSCC. Understanding these co-receptors could offer crucial insights into the molecular basis of OSCC and aid in developing targeted therapies.

4 Clinical implications of Wnt ligands and receptors in OSCC

4.1 Diagnostic biomarkers

The Wnt signaling pathway plays a crucial role in OSCC pathogenesis, with abnormal expression of its components observed in OSCC tissues versus normal oral mucosa. Dysregulated Wnt pathway activation can lead to uncontrolled cell growth, increased cell survival, and promotion of EMT, all of which are key factors in cancer development. Studies have noted changes in Wnt ligands (Wnt1, Wnt3, and Wnt5a) and receptors (FZD and LRP) in OSCC tissues compared to normal oral tissues, shedding light on the molecular mechanisms underlying this disease (Purwaningsih et al., 2021; Xie et al., 2021).

The dysregulation of the Wnt signaling pathway has been closely linked to the development and progression of OSCC. For example, the WISP1 has been found to be involved in the progression of OSCC (Xie et al., 2021). Additionally, the non-canonical Wnt/Ca^{2+}/PKC pathway, activated by Wnt5a, has been shown to promote migration and invasion in OSCC cells (Xie et al., 2021). The identification and validation of Wnt-related biomarkers for OSCC could have significant clinical implications. These biomarkers could be used as diagnostic tools to detect OSCC at an early stage, enabling timely intervention and improving patient outcomes. Furthermore, the understanding of Wnt signaling in OSCC pathogenesis may lead to the development of targeted therapies that could be integrated into the management of this disease (Bai et al., 2020; Xie et al., 2021).

One of the notable advantages of utilizing Wnt ligands and receptors as diagnostic biomarkers in OSCC is their detectability in bodily fluids, particularly serum and saliva. For example, a study found that salivary miR-30c-5p, which targets genes in the Wnt signaling pathway, was downregulated in OSCC patients compared to healthy controls (Mehterov et al., 2021). This miRNA showed good diagnostic performance with an area under curve (AUC) of 0.82. Another review discussed the potential of using salivary protein biomarkers like CA-125, which is involved in the Wnt pathway, for OSCC diagnosis and prognosis (Pekarek et al., 2023). The review also mentioned that the crosstalk between EGFR and Wnt pathways in OSCC could have diagnostic and prognostic value when assessed through salivary biomarkers.

Circulating levels of Wnt signaling components can be measured through minimally invasive blood-based assays or salivary tests, offering convenient and non-invasive approaches for early cancer detection (Sajeev et al., 2023). Studies have demonstrated promising diagnostic accuracy of Wnt ligands and receptors in discriminating OSCC patients from healthy individuals or those with benign oral lesions, underscoring their potential clinical utility in diagnostic settings.

Additionally, incorporating Wnt signaling components into biomarker panels alongside other markers or clinical data can enhance OSCC diagnostic accuracy, particularly in high-risk groups. Panels, including Wnt ligands, receptors, and relevant molecules, may improve sensitivity and specificity for OSCC detection, enabling early intervention and personalized treatments. For instance, a study on a salivary autoantibody panel showed enhanced sensitivity (63.8%) and specificity (90.0%) for early-stage OSCC detection compared to individual markers, underscoring the potential of combining Wnt-related biomarkers with other molecules to boost diagnostic performance (Hsueh et al., 2022). Additionally, longitudinal monitoring of circulating Wnt ligands and receptors during OSCC treatment and follow-up can provide valuable insights into treatment response and disease recurrence, guiding clinical decision-making and improving patient outcomes (Table 3). However, several challenges remain in the translation of Wnt signaling components into routine clinical practice as diagnostic biomarkers for OSCC (Table 3). Standardization of assays and validation in large, multicenter cohorts are imperative to establish their reliability and reproducibility.

4.2 Prognostic indicators

In OSCC, prognostic indicators play a pivotal role in predicting disease trajectory, guiding treatment strategies, and ultimately determining patient outcomes. Wnt ligands and receptors have emerged as significant prognostic indicators in OSCC, reflecting the intricate interplay between molecular signaling pathways and tumor behavior (Table 4).

Table 3 Diagnostic biomarkers for OSCC: roles of Wnt signaling components

Diagnostic biomarker	Description
Atypical expression of Wnt signaling components	Altered Wnt ligands (Wnt1, Wnt3, and Wnt5a) and receptors (FZD and LRP) in OSCC drive unchecked proliferation, increased cell viability, and EMT, contributing to pathogenesis.
WISP1 and non-canonical Wnt/Ca^{2+}/PKC pathway	WISP1 and the Wnt/Ca^{2+}/PKC pathway activated by Wnt5a drive OSCC migration and invasion. Understanding these could aid in finding biomarkers and developing targeted therapies.
Detectability in bodily fluids	Wnt ligands and receptors in bodily fluids enable non-invasive OSCC detection. Salivary biomarkers like miR-30c-5p and CA-125 distinguish OSCC patients from healthy individuals.
Blood-based assays and salivary tests	Blood and saliva tests for Wnt signaling components offer minimally invasive, accurate options for early OSCC detection and differentiation from benign lesions.
Biomarker panels	Combining Wnt signaling components with other biomarkers improves OSCC detection accuracy and facilitates early intervention and personalized treatment, especially in high-risk populations.

Wnt: Wingless/Int-1; FZD: frizzled; LRP: lipoprotein receptor-related protein; OSCC: oral squamous cell carcinoma; EMT: epithelial–mesenchymal transition; WISP1: Wnt-inducible signaling pathway protein 1; PKC: protein kinase C.

Table 4 Prognostic indicators for OSCC: roles of dysregulated Wnt signaling components

Prognostic indicator	Description
Dysregulated Wnt ligands and receptors	Dysregulated Wnt ligands (Wnt1, Wnt3, and Wnt5a) correlate with aggressive OSCC, advanced stage, larger tumors, and lymph node metastasis, leading to worse prognosis and survival.
Clinicopathological correlations	Wnt ligands and receptors correlate with OSCC tumor stage, grade, and invasion. Combining Wnt biomarkers with conventional parameters improves prognostic accuracy and risk stratification.
Therapeutic resistance mechanisms	Dysregulated Wnt signaling causes resistance to chemotherapy and radiotherapy in OSCC. Evaluating Wnt biomarkers helps identify patients at risk of resistance and recurrence, guiding personalized treatment and surveillance.
Targeting the Wnt pathway	Targeting the Wnt pathway, alone or with standard therapies, can improve OSCC treatment outcomes and overcome resistance. Evaluating Wnt components aids in personalized treatment strategies.

Wnt: Wingless/Int-1; OSCC: oral squamous cell carcinoma.

Dysregulated Wnt ligands and receptors in OSCC show a strong correlation with aggressive tumor behavior and negative clinical outcomes. Higher levels of specific Wnt proteins (Wnt1, Wnt3, and Wnt5a) are linked to advanced tumor stage, larger size, and lymph node metastasis. Wnt signaling activation drives EMT, crucial for tumor spread. Aberrant Wnt signaling accelerates invasive traits in OSCC, leading to poorer prognosis and lower survival rates. Upregulated Wnt ligands in squamous cell carcinomas, like Wnt7a, highlight the significance of the pathway in OSCC progression, notably the Wnt/β-catenin pathway (Xie et al., 2020). In addition, Wnt signaling, especially the Wnt/β-catenin pathway, actively fuels processes like EMT, which is crucial for tumor invasion and metastasis in head and neck squamous cell carcinoma (HNSCC). Wnt ligands like Wnt5a promote migration, invasion, and metastasis in HNSCC (Xie et al., 2021). This dysregulated Wnt signaling in laryngeal squamous cell carcinoma accelerates invasion and metastasis, worsening prognostic outcomes. Targeting Wnt signaling is crucial for managing OSCC.

The expression levels of Wnt ligands and receptors are significantly correlated with various clinicopathological features of OSCC, including tumor stage, grade, and lymphovascular invasion (Bueno et al., 2022; Tan et al., 2023). Assessing Wnt-related biomarkers with conventional parameters improves prognostic accuracy for OSCC. This integrated approach aids in tailored treatment plans and patient management.

Furthermore, dysregulated Wnt signaling has been implicated in therapeutic resistance mechanisms in OSCC (Xie et al., 2021). Tumors with aberrant Wnt pathway activation may display resistance to standard treatments such as chemotherapy and radiotherapy, resulting in treatment failure and disease recurrence

(Xie et al., 2021). Evaluating Wnt ligands and receptors helps identify OSCC patients at risk of treatment resistance and recurrence. Targeting the Wnt pathway, alone or with standard therapies, shows promise for improving outcomes and overcoming resistance.

5 Experimental models

5.1 In vitro models used to study Wnt signaling in OSCC

In cancer research, both in vitro and in vivo models offer distinct advantages and limitations (Fig. 2). In vitro models are indispensable in elucidating the intricate mechanisms underlying various biological processes, including the Wnt signaling pathway implicated in OSCC. OSCC-derived cell lines are cell lines that have been established from tumors or lesions of OSCC patients; they are valuable tools for studying the biology, behavior, and response of oral cancer cells to various treatments in a controlled laboratory setting (Dong et al., 2015; Lee et al., 2002). The utilization of OSCC-derived cell lines, such as SCC-9, SCC-15, CAL-27, and HSC-3, in OSCC is well-documented in the scientific literature. These cell lines are highly valuable due to their accessibility, ease of cultivation, and amenability to genetic modifications, making them ideal for studying the impacts of Wnt ligands, inhibitors, and downstream effectors on various aspects of OSCC, such as proliferation, migration, invasion, and stemness properties (Xie et al., 2021). Cell lines are crucial for understanding cancer stem cell traits and the role of Wnt signaling in OSCC, helping us explore how Wnt pathway components affect OSCC behavior and revealing intricate development mechanisms. For instance, Wnt5b elevation in metastatic OSCC cells is linked to increased migration, countered by gene silencing. Conversely, Wnt5b stimulation enhances protrusion formation in SAS-LM8 cells (Takeshita et al., 2014; Xie et al., 2021). In addition, non-canonical Wnt signaling pathways, such as the Wnt/Ca^{2+}/PKC pathway, are activated by Wnt5a, promoting migration and invasion in OSCC (Xie et al., 2021).

Three-dimensional (3D) cell culture refers to growing cells in an environment that mimics the 3D structure and conditions found in living organisms more closely than traditional two-dimensional (2D) cell cultures (Dalir Abdolahinia and Han, 2023; Urzì et al., 2023). In 3D cell culture, cells are cultured within a

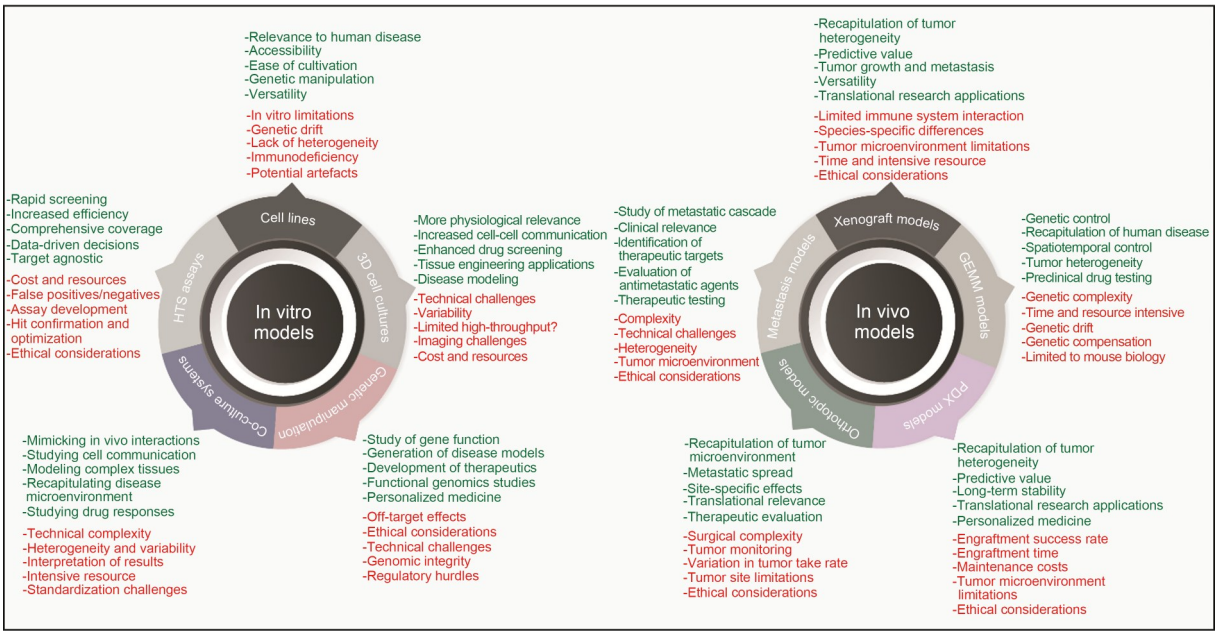

Fig. 2 Comparison of in vitro and in vivo models for studying the Wingless/Int-1 (Wnt) signaling pathway in oral squamous cell carcinoma (OSCC). Strengths (green) and weaknesses (red) of each model are highlighted. In vitro models offer controlled environments for studying specific aspects of the Wnt pathway but may lack the complexity of the in vivo tumor microenvironment. In vivo models provide a more physiologically relevant setting but can be more challenging to manipulate and may be limited in terms of accessibility and reproducibility. HTS: high-throughput screening.

scaffold or matrix, which allows them to interact with neighboring cells and the surrounding environment in a manner more akin to their natural state. Conventional monolayer cell cultures fail to recapitulate the complex microenvironment encountered by OSCC cells in vivo. To address this limitation, researchers increasingly employ 3D cell culture models, such as spheroids and organoids (Lee et al., 2023; Wanigasekara et al., 2023). For example, recent research has created a biobank of 110 head and neck cancer (HNC) organoid models, which retain key tumor DNA alterations and reflect patient responses to treatments. Organoids have shown potential for guiding treatment decisions, particularly in radiotherapy, where their response correlates with clinical outcomes. The validation of cisplatin and carboplatin as radio-sensitizers, along with the identification of the radioprotective effects of cetuximab, underscores the utility of organoids in evaluating therapeutic efficacy. Additionally, targeted treatments on organoids have suggested new therapeutic options and possible treatment stratification. Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated proteins 9 (Cas9)-based gene editing has further enhanced the roles of organoids in biomarker discovery and validation (Millen et al., 2023). These models better mimic the architecture and cell–cell interactions within OSCC tumors. Culturing OSCC cells in 3D environments enables researchers to more accurately study how Wnt signaling affects tumor growth, invasion, and response to therapy. Models like spheroids and organoids mimic OSCC tumor architecture and cell interactions, providing valuable insights into the roles of Wnt signaling in disease progression and treatment response.

Researchers can manipulate the expression levels of key Wnt signaling components using techniques like transient transfection, lentiviral transduction, or CRISPR/Cas9-mediated gene editing, which enables researchers to delineate the functional consequences of aberrant Wnt signaling in OSCC (Ai et al., 2020; Shen et al., 2023). The overexpression of Wnt components in OSCC cell lines like SCC-9, SCC-15, CAL-27, and HSC-3 helps us to explore their roles in cancer progression. Conversely, targeted knockdown allows for assessing tumor-suppressive functions and therapeutic potential. These accessible, easily cultivable cell lines facilitate in vitro studies on the impacts of Wnt signaling on OSCC proliferation, migration, invasion, and stemness.

Co-culture systems involve culturing two or more different cell types together in the same environment, allowing them to interact with each other. These systems can mimic the complex cell–cell interactions and microenvironment found in vivo, offering valuable insights into various biological processes, disease mechanisms, and therapeutic responses (Ge et al., 2023; Nguyen et al., 2023). Co-culture systems, wherein OSCC cells are cultured alongside stromal cells such as fibroblasts, endothelial cells, or immune cells, provide a more physiologically relevant platform to study Wnt signaling in the context of TME interactions (Zhang et al., 2017; Takabatake et al., 2020). These models facilitate the investigation of how Wnt signaling modulates crosstalk between OSCC cells and various stromal components, thereby influencing tumor growth, angiogenesis, immune evasion, and therapy resistance. For example, the co-culture of OSCC cells with CAFs has been shown to activate pro-inflammatory signaling pathways, including the upregulation of cytokines and chemokines like interleukin-8 (IL-8) and C-X-C motif ligand 5 (CXCL5), which are regulated by Wnt signaling (Arebro et al., 2023). Additionally, the co-culture of OSCC cells with monocyte-derived macrophages can lead to the upregulation of CC motif chemokine ligand 2 (CCL2) and CC-chemokine receptor 2 (CCR2) expression, which is mediated by the Wnt signaling regulator kinesin superfamily protein 4A (Kif4A) (Zhang et al., 2017).

High-throughput screening (HTS) is a method used in drug discovery and chemical biology to rapidly test large numbers of compounds or molecules for their biological activity or therapeutic potential. The goal of HTS is to identify lead compounds that could serve as starting points for drug development or further optimization (Cadena et al., 2023; Verrelle et al., 2024). HTS assays enable the rapid and systematic evaluation of large compound libraries to identify novel regulators of Wnt signaling (Grimaldi et al., 2018). Utilizing reporter gene assays, such as T-cell factor reporter plasmid (TOPFlash) or TCF/LEF luciferase assay, researchers can assess the transcriptional activity of Wnt-responsive genes in response to small-molecule inhibitors, activators, or natural compounds. These HTS platforms facilitate the discovery of potential therapeutic agents targeting aberrant Wnt signaling pathways in OSCC. For example, HTS for Wnt/β-catenin signaling pathway modulators identified pyrithione

zinc (PYZ) as a potent inhibitor of Wnt/β-catenin signaling in OSCC cells (Srivastava et al., 2015). PYZ was found to decrease the expression of key Wnt signaling components, including β-catenin, TCF1, LEF1, cyclin D1, and c-Myc, leading to the inhibition of OSCC cell proliferation and tumor growth (Srivastava et al., 2015). An HTS cell model for OSCC, utilizing a TOPFlash reporter assay, quantifies Wnt/β-catenin transcriptional activity and aids in identifying therapeutic targets and compounds to regulate Wnt signaling in OSCC. Combined with reporter gene assays, 3D cultures, and co-culture systems, these platforms provide a comprehensive approach to studying the role of Wnt signaling in OSCC and discovering potential therapies.

5.2 In vivo models and their relevance to understanding Wnt signaling in OSCC

In vivo models are essential for comprehensively understanding the relevance of Wnt signaling in OSCC. Xenograft model is a type of preclinical animal model used in cancer research to study the growth and behavior of human tumors in vivo. In xenograft models, human tumor cells or tissues are implanted or injected into immunodeficient mice or other animals, allowing researchers to study various aspects of tumor biology, progression, and response to treatment. Xenograft models involve the transplantation of human OSCC cells into immunocompromised mice, typically via subcutaneous or orthotopical implantation in the oral cavity (Menon et al., 2017). These models enable the study of tumor growth, invasion, and metastasis in vivo. By modulating the expression of Wnt signaling components in OSCC cells prior to transplantation, researchers can assess the impacts of aberrant Wnt signaling on tumor behavior and response to therapy (Liu et al., 2018; Hou et al., 2024). For example, a study using a xenograft model demonstrated that overexpression of the Wnt target gene *CDK5RAP2* in OSCC cells led to increased tumor growth, invasion, and stemness properties. Conversely, knockdown of *CDK5RAP2* inhibited these malignant behaviors, highlighting the crucial role of Wnt signaling in OSCC progression (Shen et al., 2023). Additionally, xenograft models are used to evaluate Wnt-targeted therapies' efficacy against OSCC progression. Researchers employ these in vivo models to test inhibitors like small molecules or antibodies and gauge their potential as OSCC treatments. These models offer a comprehensive strategy for understanding how Wnt signaling drives OSCC development and identifying potential therapeutic targets within the pathway.

Genetically engineered mouse models (GEMMs) involve mice that have been genetically modified to carry specific mutations or alterations in their genome, often to mimic human diseases such as cancer. These models are valuable tools in biomedical research for studying the underlying mechanisms of disease, testing potential therapeutics, and exploring gene function in vivo (Walrath et al., 2010). GEMMs provide a valuable in vivo platform for studying Wnt signaling in OSCC by mimicking the stepwise accumulation of genetic alterations observed in human OSCC (Walrath et al., 2010; Li et al., 2020). These models allow researchers to investigate the roles of Wnt signaling in tumor initiation, progression, and metastasis within an intact immune system and TME. For example, *K14-Cre; Ctnnb1*$^{ex3/+}$ mice harbor activating mutations in β-catenin, which leads to the development of OSCC with features such as hyperplasia, hyperkeratosis, severe epithelial dysplasia, and cancer (Tasoulas et al., 2023). GEMMs provide a faithful representation of human OSCC development, facilitating the study of the impact of aberrant Wnt signaling on tumor behavior and therapy response. GEMMs enable preclinical testing of Wnt-targeted therapies and help with understanding the mechanisms of therapy resistance. They provide insights into the interplay among Wnt signaling, the immune system, and the TME in OSCC development and progression.

Patient-derived xenografts (PDX) are preclinical models used in cancer research that involve the transplantation of tumor tissue directly from cancer patients into immunodeficient mice. These models aim to replicate the biological characteristics and heterogeneity of human tumors more accurately than traditional cell line-based xenograft models (Invrea et al., 2020; Zanella et al., 2022). PDX models are valuable in vivo tools for translational research in OSCC, involving the transplantation of patient-derived OSCC tumor tissues directly into immunocompromised mice, preserving the histological and molecular heterogeneity of the original patient tumors (Silveira et al., 2023). By engrafting OSCC tumors with known Wnt signaling alterations, such as mutations in β-catenin or adenomatous polyposis coli (APC), researchers can investigate

their impacts on tumor behavior and response to therapy in vivo. PDX models may facilitate the identification of patient-specific therapeutic vulnerabilities and the evaluation of personalized treatment strategies targeting aberrant Wnt signaling pathways. These models maintain the original tumor architecture, allowing for the study of tumor growth, invasion, and metastasis in a more physiologically relevant context compared to cell lines (Liu et al., 2023). Researchers can utilize PDX models to study the impacts of Wnt signaling alterations on tumor behavior and response to therapy in vivo, providing valuable insights into the potential therapeutic targets and personalized treatment strategies for OSCC patients.

Orthotopic implantation models are in vivo models. This model can be used to study Wnt signaling in OSCC. These models involve the inoculation of OSCC cells directly into the oral cavity of immunocompromised mice, mimicking the anatomical site of human OSCC development. By modulating Wnt signaling in OSCC cells prior to implantation, researchers can investigate how dysregulated Wnt signaling influences tumor–stroma interactions, angiogenesis, and immune evasion in vivo (Vahle et al., 2012; Chaves et al., 2023). Orthotopic implantation models provide a platform for evaluating novel therapeutic strategies targeting the Wnt signaling pathway in the context of primary OSCC tumors. These models enable the study of tumor growth, invasion, and metastasis within the context of the oral microenvironment, providing valuable insights into the impacts of Wnt signaling alterations on tumor behavior and response to therapy in vivo (Bais et al., 2015).

Metastasis models are preclinical models used in cancer research to study the process by which cancer cells spread from the primary tumor to distant sites in the body, forming secondary tumors. Understanding the mechanisms of metastasis is crucial for developing effective treatments to prevent or target metastatic disease, which is the primary cause of cancer-related mortality (Zhang et al., 2021). These models are vital for understanding and predicting metastasis, a significant factor affecting patient prognosis. The studies discuss combining variables like gene profiles, clinical parameters, and molecular factors to create accurate prediction models for nodal metastasis in OSCC. Notably, the combination of cyclin-dependent kinase inhibitor 2A (CDKN2A), urokinase-type plasminogen activator (PLAU), T stage, and pathological grade has been highlighted as an effective predictive model for lymph node metastasis in OSCC (Xu et al., 2023). In the context of in vivo metastasis models for OSCC, the search results primarily focus on orthotopic mouse models. These models involve injecting tumor cells into the tongues of mice to induce local tumor growth and metastasis. The models using non-metastatic CAL-27 cells and metastatic UMSCC2 cells have been developed to reflect tumor growth and metastasis in OSCC. These models provide valuable insights into the mechanisms of OSCC growth and metastasis, aiding in evaluating potential therapeutics (Bais et al., 2015). Overall, the combination of predictive models based on gene profiles, clinical parameters, and molecular factors, along with the development of orthotopic mouse models, plays a crucial role in advancing our understanding of OSCC metastasis and developing effective therapeutic strategies to combat this challenging aspect of the disease.

6 Therapeutic targets and strategies

Exploring therapeutic targets and strategies involving the Wnt signaling pathway in OSCC is essential for developing effective treatments. By targeting specific components of the Wnt signaling pathway and employing diverse therapeutic strategies, researchers aim to develop innovative treatments that effectively inhibit OSCC progression and improve patient outcomes (Fig. 3).

6.1 Wnt ligand inhibition

Targeting Wnt ligands directly represents a promising therapeutic strategy for disrupting the intricate signaling pathways involved in OSCC progression. Wnt ligands are pivotal components of the Wnt signaling pathway, orchestrating cellular processes critical for tumor growth and metastasis. In OSCC, dysregulated Wnt ligand secretion fuels autocrine and paracrine signaling loops, fostering malignant transformation and disease progression (Patel et al., 2019). Therefore, inhibiting Wnt ligand secretion is a viable therapeutic approach to impede OSCC progression.

Porcupine is an essential enzyme for Wnt ligand secretion and catalyzes the post-translational modification of Wnt ligands necessary for their secretion and activation. Small-molecule inhibitors targeting porcupine have demonstrated efficacy in preclinical

Fig. 3 Various therapeutic strategies for treating oral squamous cell carcinoma (OSCC). Wnt: Wingless/Int-1; EGFR: epidermal growth factor receptor; LRP5/6: lipoprotein receptor-related protein 5/6; FZD: frizzled.

models of OSCC (Peña-Oyarzún et al., 2024). Notably, LGK974 is a potent and selective inhibitor of porcupine that has shown promise in inhibiting Wnt ligand secretion and downstream signaling cascades. By inhibiting porcupine activity, LGK974 effectively disrupts the secretion of Wnt ligands, thus attenuating Wnt signaling activation and suppressing tumor growth in OSCC. The mechanism of action of porcupine inhibitors like LGK974 involves binding to the active site of porcupine, which blocks its enzymatic activity and prevents the palmitoylation of Wnt ligands. Palmitoylation is a lipid modification critical for the secretion and proper functioning of Wnt ligands (Liu et al., 2013). By inhibiting porcupine-mediated palmitoylation, LGK974 effectively impedes the secretion of Wnt ligands into the extracellular environment, disrupting both autocrine and paracrine Wnt signaling loops in OSCC. Preclinical studies evaluating the efficacy of porcupine inhibitors in OSCC have shown promising results. Treatment with LGK974 has been shown to inhibit cell proliferation, induce apoptosis, and suppress tumor growth in xenograft models (Paluszczak, 2020; Reyes et al., 2020).

While porcupine inhibitors such as LGK974 hold promise as OSCC therapies, further research is needed into their safety, pharmacokinetics, and side effects in clinical use. Biomarker-driven trials are required to optimize treatment strategies and identify the patient groups that benefit the most. Targeting Wnt secretion via porcupine inhibition offers a promising approach to disrupting Wnt signaling and combating OSCC progression.

6.2 Frizzled receptor inhibition

FZDs are crucial mediators of the Wnt signaling pathway, which play a pivotal role in the pathogenesis of OSCC (Zeng et al., 2018; Sompel et al., 2021). Aberrant activation of the Wnt/FZD signaling axis has been implicated in the development and progression of OSCC, making FZDs attractive therapeutic targets (Smith et al., 2021; Xie et al., 2021).

Blocking the interaction between FZDs and their cognate Wnt ligands can effectively inhibit downstream signaling cascades, thereby preventing the malignant transformation and proliferation of OSCC cells (Zhang et al., 2015; Zeng et al., 2018). One promising

approach is the use of monoclonal antibodies that specifically target individual FZD receptors. These antibodies can bind to the extracellular domain of FZDs, preventing Wnt ligand binding and subsequent activation of the Wnt signaling pathway (Zeng et al., 2018; Smith et al., 2021).

In addition to monoclonal antibodies, small-molecule inhibitors that interfere with the FZD receptor–ligand interaction have also been explored as potential therapeutic strategies for OSCC. These small molecules can disrupt the formation of the FZD-Wnt complex, effectively blocking the initiation of Wnt signaling and its downstream effects on cell proliferation, migration, and invasion (Sompel et al., 2021; Xie et al., 2021).

6.3 LRP receptor inhibition

The LRPs, particularly LRP5 and LRP6, are essential co-receptors in the Wnt signaling pathway, which are aberrantly activated in OSCC. The formation of the Wnt-FZD-LRP complex is a critical step in the initiation of Wnt signaling, making LRP5/6 receptors attractive therapeutic targets for OSCC. Inhibiting the activity of LRP5/6 receptors can effectively disrupt the Wnt-FZD-LRP complex, preventing the downstream activation of Wnt signaling cascades. This approach can lead to the suppression of various malignant phenotypes associated with OSCC, such as uncontrolled cell proliferation, migration, and invasion (Yuan et al., 2017; Hsu et al., 2019).

Several strategies have been explored to target LRP receptors in OSCC. Small-molecule inhibitors that bind to and block the extracellular domain of LRP have shown promising results in preclinical studies (Robert et al., 2018). These inhibitors can effectively interfere with the interaction between Wnt ligands and LRP receptors, preventing the activation of Wnt signaling.

6.4 β-Catenin inhibition

β-Catenin is a central mediator of the canonical Wnt signaling pathway, which plays a crucial role in the pathogenesis of OSCC (Robert et al., 2018). As a key transcriptional regulator, β-catenin drives the expression of target genes involved in various oncogenic processes, such as cell proliferation, survival, and metastasis (Kim et al., 2019; Wang et al., 2021).

The inhibition of β-catenin activity has been identified as a promising therapeutic approach for OSCC. Preclinical studies have demonstrated encouraging findings regarding small-molecule inhibitors that selectively focus on β-catenin or impede its interaction with transcriptional co-activators, including CREBBP (Chandler et al., 2020; Reyes et al., 2020).

One such small-molecule inhibitor, ICG-001, has been found to effectively inhibit the β-catenin–CBP interaction, leading to the suppression of EGFR oncogenic activity in OSCC cells. By disrupting this critical signaling axis, ICG-001 can reduce the malignant phenotype of OSCC, including cell proliferation, migration, and invasion. Similarly, another small-molecule inhibitor, E7386, has also been shown to target the β-catenin–CBP interaction, resulting in increased expression of fucosyltransferases and enhanced EGFR *N*-glycan antennary fucosylation. This modification of EGFR glycosylation can potentially impact its oncogenic signaling and contribute to the anti-tumor effects of β-catenin inhibition (Chandler et al., 2020).

These studies highlight the therapeutic potential of targeting the β-catenin signaling axis in OSCC. By disrupting the aberrant activation of β-catenin and its downstream transcriptional programs, small-molecule inhibitors can effectively suppress Wnt-driven oncogenic processes and offer a promising approach for the management of this disease.

6.5 Combination therapies

Emerging evidence suggests that combining Wnt pathway inhibitors with standard chemotherapeutic agents, targeted therapies, or immunotherapies may enhance treatment efficacy in OSCC (Meng et al., 2021; Silva et al., 2023). The aberrant activation of the Wnt signaling pathway is a key driver of OSCC pathogenesis, and targeting this pathway in combination with other therapeutic modalities has shown promising results in preclinical studies.

One potential combination strategy could be the use of Wnt pathway inhibitors alongside EGFR-targeted therapies. EGFR is a crucial signaling node in OSCC, and its inhibition can effectively suppress tumor progression. However, resistance to EGFR-targeted therapies often develops, and the combination with Wnt pathway inhibitors may help overcome this challenge. Preclinical studies have demonstrated that the inhibition of Wnt signaling—for example, by targeting FZD receptors or β-catenin—can sensitize OSCC cells to EGFR-targeted therapies, leading to enhanced anti-tumor effects (Silva et al., 2023).

Another promising combination approach is using Wnt pathway inhibitors in conjunction with immune checkpoint inhibitors. The Wnt/β-catenin pathway has been implicated in the modulation of the TME and immune evasion in OSCC. By combining Wnt inhibitors with immune checkpoint blockade, researchers have observed synergistic effects in preclinical models, leading to improved tumor control and increased immune cell infiltration.

Furthermore, the combination of Wnt pathway inhibitors with standard chemotherapeutic agents, such as cisplatin or 5-fluorouracil, has also been explored in OSCC. Preclinical studies have shown that the inhibition of Wnt signaling can sensitize OSCC cells to the cytotoxic effects of these chemotherapeutic drugs, resulting in enhanced anti-tumor activity and reduced drug resistance.

These combination approaches targeting the Wnt pathway in conjunction with other therapeutic modalities have the potential to improve treatment outcomes in OSCC. However, further research and clinical trials are necessary to fully evaluate the efficacy and safety of using these combination therapies in the management of this disease.

6.6 Precision medicine approaches

Precision medicine strategies offer significant potential for managing OSCC by using molecular profiling of tumors to inform personalized treatment choices (Zhong et al., 2018). The aberrant activation of the Wnt signaling pathway has been widely implicated in the pathogenesis of OSCC. Molecular profiling of OSCC tumors can identify patients with specific genetic or epigenetic alterations in Wnt pathway components, such as dysregulated expression of Wnt ligands, FZD receptors, LRP co-receptors, or β-catenin. By recognizing these molecular subtypes of OSCC, clinicians can select targeted therapies that specifically inhibit the Wnt signaling axis, potentially optimizing therapeutic efficacy and minimizing adverse effects (Patil and Nagaraju, 2021; Silva et al., 2023).

Biomarker-driven clinical trials evaluating the efficacy of Wnt pathway inhibitors in molecularly defined subgroups of OSCC patients are essential for validating the therapeutic potential of these targeted approaches. These trials can assess the clinical benefit of Wnt inhibitors, such as FZD receptor antagonists, LRP inhibitors, or β-catenin inhibitors, in patients whose tumors exhibit specific Wnt pathway alterations. By identifying biomarkers that predict treatment response, these studies can help guide the selection of those OSCC patients most likely to benefit from Wnt-targeted therapies (Patil and Nagaraju, 2021; Silva et al., 2023).

Furthermore, the integration of Wnt pathway inhibitors with other treatment modalities, such as chemotherapy, EGFR-targeted agents, or immunotherapy, may enhance the efficacy of precision medicine approaches in OSCC. Combination therapies that simultaneously target multiple oncogenic signaling pathways can potentially overcome therapeutic resistance and improve clinical outcomes for patients with Wnt-driven OSCC.

Overall, the molecular profiling of OSCC tumors and the development of biomarker-driven clinical trials that evaluate Wnt pathway inhibitors represent crucial steps toward implementing precision medicine for this disease. By tailoring treatments to the individual tumor characteristics, clinicians can optimize therapeutic strategies and improve the quality of care for OSCC patients.

7 Challenges and future perspectives

Current research on the role of Wnt ligands and receptors in OSCC faces several limitations that hinder the translation of findings into clinical practice. One major challenge is the inherent heterogeneity of OSCC, both intertumoral and intratumoral. This diversity complicates targeted therapy development, as treatments may not effectively address all subtypes of OSCC, leading to inconsistent treatment responses and limited clinical efficacy (Patel et al., 2019). Additionally, the lack of robust biomarkers for OSCC further impedes progress in this field. Many studies rely on small sample sizes and lack validation in larger patient cohorts, undermining the reliability and generalizability of findings.

Therapeutic resistance poses another significant obstacle in OSCC treatment (Sa et al., 2024; Zhao et al., 2024). Despite advancements in targeting Wnt pathways, resistance mechanisms remain poorly understood. This lack of understanding limits the effectiveness of targeted therapies and necessitates further investigation into alternative treatment modalities and combination therapies. In addition, the translation of preclinical findings into clinical applications is hindered by the limitations of existing preclinical models,

which often fail to fully replicate the complex TME and molecular heterogeneity of OSCC. This highlights the need for more representative and clinically relevant model systems to improve the predictive value of preclinical studies.

Emerging technologies and methodologies offer promising solutions to overcome the limitations of current research on Wnt ligands and receptors in OSCC. Single-cell analysis, for instance, provides a comprehensive understanding of cellular heterogeneity within OSCC tumors, facilitating the identification of rare cell populations and signaling pathways (Sun et al., 2023; Yang et al., 2023). The integration of omics technologies, such as genomics, transcriptomics, proteomics, and metabolomics, enables a holistic view of the molecular landscape of OSCC, aiding in the identification of dysregulated Wnt signaling pathways and potential therapeutic targets. Additionally, CRISPR/Cas9 genome editing allows for precise manipulation of the genome to elucidate the functional significance of Wnt pathway alterations in OSCC progression.

Furthermore, patient-derived organoid models offer a valuable platform for drug screening and personalized medicine approaches. These models faithfully recapitulate the histological and molecular features of OSCC tumors, enabling the evaluation of therapeutic responses in a patient-specific context. Organoid models hold promise for identifying effective treatment strategies tailored to individual patient profiles, thereby advancing personalized medicine in OSCC management (Farshbaf et al., 2023).

Targeting Wnt ligands and receptors presents significant opportunities for the development of targeted therapies in OSCC. Small-molecule inhibitors and monoclonal antibodies directed against key components of the Wnt pathway demonstrate efficacy in preclinical models and hold potential for clinical translation. Biomarker-guided therapy, integrating molecular biomarkers into clinical practice, enables personalized treatment selection and optimization of therapeutic regimens based on individual patient characteristics. This approach enhances treatment efficacy and minimizes unnecessary treatment-related toxicities.

Additionally, immunotherapeutic approaches such as immune checkpoint inhibitors have shown promise in OSCC treatment. Modulation of the immune microenvironment by targeting Wnt signaling pathways may enhance the efficacy of immunotherapy and overcome resistance mechanisms. Precision oncology trials incorporating comprehensive molecular profiling and targeted therapeutic interventions are essential for advancing personalized medicine in OSCC. These trials enable the real-time adaptation of treatment strategies based on genomic data, biomarker analysis, and therapeutic response monitoring, which maximizes therapeutic efficacy and improves patient outcomes in OSCC.

8 Conclusions

In conclusion, the roles of Wnt ligands and receptors in OSCC are increasingly recognized as pivotal in driving tumorigenesis and progression. Through intricate signaling cascades, the aberrant activation of Wnt pathways contributes to key hallmarks of cancer, including proliferation, invasion, and metastasis in OSCC. In addition, dysregulation of Wnt signaling has been implicated in the maintenance of cancer stem cell populations, further emphasizing its significance in OSCC pathogenesis. Targeting Wnt signaling components presents a promising therapeutic strategy for OSCC treatment, with the potential for both direct inhibition of tumorigenic pathways and synergistic effects with existing therapies. However, the complexity of Wnt signaling networks underscores the need for a comprehensive understanding of context-specific interactions and feedback mechanisms within OSCC microenvironments. Future research efforts should focus on elucidating the precise roles of individual Wnt ligands and receptors in OSCC progression, as well as exploring combinatorial therapeutic approaches to effectively target Wnt signaling and improve clinical outcomes for OSCC patients.

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Author contributions

Muhammad TUFAIL performed the conceptualization, original drafting, visualization, and writing – review & editing. Caiyun HE performed the conceptualization, visualization, revisions, and editing. Canhua JIANG contributed to the visualization. Ning LI performed the supervision and writing – review & editing. All authors have reviewed and approved the final manuscript for publication.

Compliance with ethics guidelines

Muhammad TUFAIL, Caiyun HE, Canhua JIANG, and Ning LI declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

References

Ai YL, Wu SY, Zou C, et al., 2020. LINC00941 promotes oral squamous cell carcinoma progression via activating CAPRIN2 and canonical WNT/β-catenin signaling pathway. *J Cell Mol Med*, 24(18):10512-10524. https://doi.org/10.1111/jcmm.15667

Arebro J, Towle R, Lee CM, et al., 2023. Extracellular vesicles promote activation of pro-inflammatory cancer-associated fibroblasts in oral cancer. *Front Cell Dev Biol*, 11:1240159. https://doi.org/10.3389/fcell.2023.1240159

Bai YP, Sha JJ, Kanno T, 2020. The role of carcinogenesis-related biomarkers in the Wnt pathway and their effects on epithelial–mesenchymal transition (EMT) in oral squamous cell carcinoma. *Cancers*, 12(3):555. https://doi.org/10.3390/cancers12030555

Bais MV, Kukuruzinska M, Trackman PC, 2015. Orthotopic non-metastatic and metastatic oral cancer mouse models. *Oral Oncol*, 51(5):476-482. https://doi.org/10.1016/j.oraloncology.2015.01.012

Bueno MLP, Saad STO, Roversi FM, 2022. WNT5A in tumor development and progression: a comprehensive review. *Biomed Pharmacother*, 155:113599. https://doi.org/10.1016/j.biopha.2022.113599

Cadena IA, Buchanan MR, Harris CG, et al., 2023. Engineering high throughput screening platforms of cervical cancer. *J Biomed Mater Res*, 111(6):747-764. https://doi.org/10.1002/jbm.a.37522

Cadigan KM, Waterman ML, 2012. TCF/LEFs and Wnt signaling in the nucleus. *Cold Spring Harb Perspect Biol*, 4(11): a007906. https://doi.org/10.1101/cshperspect.a007906

Chandler KB, Alamoud KA, Stahl VL, et al., 2020. β-Catenin/CBP inhibition alters epidermal growth factor receptor fucosylation status in oral squamous cell carcinoma. *Mol Omics*, 16(3):195-209. https://doi.org/10.1039/d0mo00009d

Chaves P, Garrido M, Oliver J, et al., 2023. Preclinical models in head and neck squamous cell carcinoma. *Br J Cancer*, 128(10):1819-1827. https://doi.org/10.1038/s41416-023-02186-1

Chen C, Luo LN, Xu CL, et al., 2022. Tumor specificity of WNT ligands and receptors reveals universal squamous cell carcinoma oncogenes. *BMC Cancer*, 22:790. https://doi.org/10.1186/s12885-022-09898-2

Cierpikowski P, Lis-Nawara A, Bar J, 2023. Prognostic value of WNT1, NOTCH1, PDGFRβ, and CXCR4 in oral squamous cell carcinoma. *Anticancer Res*, 43(2):591-602. https://doi.org/10.21873/anticanres.16195

Dalir Abdolahinia E, Han XZ, 2023. The three-dimensional in vitro cell culture models in the study of oral cancer immune microenvironment. *Cancers*, 15(17):4266. https://doi.org/10.3390/cancers15174266

Dong Y, Zhao Q, Ma XY, et al., 2015. Establishment of a new OSCC cell line derived from OLK and identification of malignant transformation-related proteins by differential proteomics approach. *Sci Rep*, 5:12668. https://doi.org/10.1038/srep12668

Farrapo MT, Rifane TO, Pinto DN, et al., 2022. Canonical WNT signaling pathway in oral squamous cell carcinoma prognosis. *Res Soc Dev*, 11(2):e8411225462. https://doi.org/10.33448/rsd-v11i2.25462

Farshbaf A, Lotfi M, Zare R, et al., 2023. The organoid as reliable cancer modeling in personalized medicine, does applicable in precision medicine of head and neck squamous cell carcinoma? *Pharmacogenomics J*, 23(2-3):37-44. https://doi.org/10.1038/s41397-022-00296-2

Fleming-de-Moraes CD, Rocha MR, Tessmann JW, et al., 2022. Crosstalk between PI3K/Akt and Wnt/β-catenin pathways promote colorectal cancer progression regardless of mutational status. *Cancer Biol Ther*, 23(1):1-13. https://doi.org/10.1080/15384047.2022.2108690

Ge C, Huang XT, Zhang SJ, et al., 2023. In vitro co-culture systems of hepatic and intestinal cells for cellular pharmacokinetic and pharmacodynamic studies of capecitabine against colorectal cancer. *Cancer Cell Int*, 23:14. https://doi.org/10.1186/s12935-023-02853-6

Grimaldi M, Boulahtouf A, Prévostel C, et al., 2018. A cell model suitable for a high-throughput screening of inhibitors of the Wnt/β-catenin pathway. *Front Pharmacol*, 9:1160. https://doi.org/10.3389/fphar.2018.01160

He K, Gan WJ, 2023. Wnt/β-catenin signaling pathway in the development and progression of colorectal cancer. *Cancer Manag Res*, 15:435-448. https://doi.org/10.2147/cmar.S411168

Hou ZY, Wu CZ, Tang JR, et al., 2024. CLSPN actives Wnt/β-catenin signaling to facilitate glycolysis and cell proliferation in oral squamous cell carcinoma. *Exp Cell Res*, 435(2): 113935. https://doi.org/10.1016/j.yexcr.2024.113935

Hsu TN, Huang CM, Huang CS, et al., 2019. Targeting FAT1 inhibits carcinogenesis, induces oxidative stress and enhances cisplatin sensitivity through deregulation of LRP5/WNT2/GSS signaling axis in oral squamous cell carcinoma. *Cancers*, 11(12):1883. https://doi.org/10.3390/cancers11121883

Hsueh PC, Chang KP, Liu HP, et al., 2022. Development of a salivary autoantibody biomarker panel for diagnosis of oral cavity squamous cell carcinoma. *Front Oncol*, 12:968570. https://doi.org/10.3389/fonc.2022.968570

Invrea F, Rovito R, Torchiaro E, et al., 2020. Patient-derived xenografts (PDXs) as model systems for human cancer. *Curr Opin Biotechnol*, 63:151-156. https://doi.org/10.1016/j.copbio.2020.01.003

Jia B, Qiu XL, Chu HX, et al., 2019. Wnt7a predicts poor prognosis, and contributes to growth and metastasis in tongue squamous cell carcinoma. *Oncol Rep*, 41(3):1749-1758. https://doi.org/10.3892/or.2019.6974

Joiner DM, Ke JY, Zhong ZD, et al., 2013. LRP5 and LRP6 in development and disease. *Trends Endocrinol Metab*, 24(1):

31-39.
https://doi.org/10.1016/j.tem.2012.10.003

Jung EK, Kim SA, Yoon TM, et al., 2017. WNT1-inducible signaling pathway protein-1 contributes to tumor progression and treatment failure in oral squamous cell carcinoma. *Oncol Lett*, 14(2):1719-1724.
https://doi.org/10.3892/ol.2017.6313

Kalinke LP, Alvares LE, Schussel JL, et al., 2016. Expression of *WNT10A* gene in oral squamous cell carcinoma. *West Indian Med J*, 65(3):480-485.
https://doi.org/10.7727/wimj.2014.347

Kartha VK, Alamoud KA, Sadykov K, et al., 2018. Functional and genomic analyses reveal therapeutic potential of targeting β-catenin/CBP activity in head and neck cancer. *Genome Med*, 10:54.
https://doi.org/10.1186/s13073-018-0569-7

Kayamori K, Katsube KI, Hirai H, et al., 2023. Role of stromal fibroblast-induced WNT7A associated with cancer cell migration through the AKT/CLDN1 signaling axis in oral squamous cell carcinoma. *Lab Invest*, 103(10):100228.
https://doi.org/10.1016/j.labinv.2023.100228

Kim O, Ahn K, Kim HE, et al., 2019. Screening of β-catenin inhibitor from medicinal plant extracts for intractable recurrent oral cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol*, 128(1):e43.
https://doi.org/10.1016/j.oooo.2019.02.086

Krisanaprakornkit S, Iamaroon A, 2012. Epithelial-mesenchymal transition in oral squamous cell carcinoma. *Int Scholarly Res Not*, 2012:681469.
https://doi.org/10.5402/2012/681469

Kumar V, Vashishta M, Kong L, et al., 2021. The role of notch, hedgehog, and Wnt signaling pathways in the resistance of tumors to anticancer therapies. *Front Cell Dev Biol*, 9: 650772.
https://doi.org/10.3389/fcell.2021.650772

Lau HK, Wu ER, Chen MK, et al., 2017. Effect of genetic variation in microRNA binding site in WNT1-inducible signaling pathway protein 1 gene on oral squamous cell carcinoma susceptibility. *PLoS ONE*, 12(4):e0176246.
https://doi.org/10.1371/journal.pone.0176246

Lee G, Kim YB, Kim JH, et al., 2002. Characterization of novel cell lines established from three human oral squamous cell carcinomas. *Int J Oncol*, 20(6):1151-1159.

Lee SY, Koo IS, Hwang HJ, et al., 2023. *In vitro* three-dimensional (3D) cell culture tools for spheroid and organoid models. *SLAS Discov*, 28(4):119-137.
https://doi.org/10.1016/j.slasd.2023.03.006

Li Q, Dong H, Yang GW, et al., 2020. Mouse tumor-bearing models as preclinical study platforms for oral squamous cell carcinoma. *Front Oncol*, 10:212.
https://doi.org/10.3389/fonc.2020.00212

Liu BY, Chen W, Cao G, et al., 2017. MicroRNA-27b inhibits cell proliferation in oral squamous cell carcinoma by targeting FZD7 and Wnt signaling pathway. *Arch Oral Biol*, 83:92-96.
https://doi.org/10.1016/j.archoralbio.2017.07.009

Liu BY, Cao G, Dong Z, et al., 2019. Effect of microRNA-27b on cisplatin chemotherapy sensitivity of oral squamous cell carcinoma via FZD7 signaling pathway. *Oncol Lett*, 18(1):667-673.
https://doi.org/10.3892/ol.2019.10347

Liu J, Pan SF, Hsieh MH, et al., 2013. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. *Proc Natl Acad Sci USA*, 110(50):20224-20229.
https://doi.org/10.1073/pnas.1314239110

Liu LJ, Jiang H, Zhao J, et al., 2018. MiRNA-16 inhibited oral squamous carcinoma tumor growth in vitro and in vivo via suppressing Wnt/β-catenin signaling pathway. *Onco Targets Ther*, 11:5111-5119.
https://doi.org/10.2147/OTT.S153888

Liu YH, Wu WT, Cai CJ, et al., 2023. Patient-derived xenograft models in cancer therapy: technologies and applications. *Signal Transduct Target Ther*, 8:160.
https://doi.org/10.1038/s41392-023-01419-2

Ma JT, Ren YP, Zhang L, et al., 2017. Knocking-down of CREPT prohibits the progression of oral squamous cell carcinoma and suppresses cyclin D1 and c-Myc expression. *PLoS ONE*, 12(4):e0174309.
https://doi.org/10.1371/journal.pone.0174309

Mehterov N, Vladimirov B, Sacconi A, et al., 2021. Salivary miR-30c-5p as potential biomarker for detection of oral squamous cell carcinoma. *Biomedicines*, 9(9):1079.
https://doi.org/10.3390/biomedicines9091079

Meng X, Lou QY, Yang WY, et al., 2021. The role of non-coding RNAs in drug resistance of oral squamous cell carcinoma and therapeutic potential. *Cancer Commun (Lond)*, 41(10):981-1006.
https://doi.org/10.1002/cac2.12194

Menon R, Li CC, Li MZ, 2017. Wnt signaling in oral cancer initiating cells. *Oral Surg Oral Med Oral Pathol Oral Radiol*, 124(3):e202.
https://doi.org/10.1016/j.oooo.2017.06.015

Millen R, de Kort WWB, Koomen M, et al., 2023. Patient-derived head and neck cancer organoids allow treatment stratification and serve as a tool for biomarker validation and identification. *Med*, 4(5):290-310.e12.
https://doi.org/10.1016/j.medj.2023.04.003

Min AJ, Zhu C, Peng SP, et al., 2016. Downregulation of microRNA-148a in cancer-associated fibroblasts from oral cancer promotes cancer cell migration and invasion by targeting Wnt10b. *J Biochem Mol Toxicol*, 30(4):186-191.
https://doi.org/10.1002/jbt.21777

Ngernsombat C, Prattapong P, Larbcharoensub N, et al., 2021. WNT8B as an independent prognostic marker for nasopharyngeal carcinoma. *Curr Oncol*, 28(4):2529-2539.
https://doi.org/10.3390/curroncol28040230

Nguyen NT, Doan VN, Tran HLB, 2023. Role of co-culture with fibroblasts and dynamic culture systems in 3-dimensional MCF-7 tumor model maturation. *Trends Sci*, 20(2):3892-3892.
https://doi.org/10.48048/tis.2023.3892

Nie XB, Liu HY, Liu L, et al., 2020. Emerging roles of Wnt ligands in human colorectal cancer. *Front Oncol*, 10:1341.
https://doi.org/10.3389/fonc.2020.01341

Noguti J, de Moura CFG, Hossaka TA, et al., 2012. The role of canonical WNT signaling pathway in oral carcinogenesis:

a comprehensive review. *Anticancer Res*, 32(3):873-878.

Paluszczak J, 2020. The significance of the dysregulation of canonical Wnt signaling in head and neck squamous cell carcinomas. *Cells*, 9(3):723. https://doi.org/10.3390/cells9030723

Patel S, Alam A, Pant R, et al., 2019. Wnt signaling and its significance within the tumor microenvironment: novel therapeutic insights. *Front Immunol*, 10:2872. https://doi.org/10.3389/fimmu.2019.02872

Patil DJ, Nagaraju R, 2021. Personalised precision medicine - a novel approach for oral cancer management. *In*: Sridharan G (Ed.), Oral Cancer—Current Concepts and Future Perspectives. IntechOpen, Rijeka. https://doi.org/10.5772/intechopen.99558

Pekarek L, Garrido-Gil MJ, Sánchez-Cendra A, et al., 2023. Emerging histological and serological biomarkers in oral squamous cell carcinoma: applications in diagnosis, prognosis evaluation and personalized therapeutics (Review). *Oncol Rep*, 50(6):213. https://doi.org/10.3892/or.2023.8650

Peña-Oyarzún D, Flores T, Torres VA, et al., 2024. Inhibition of PORCN blocks Wnt signaling to attenuate progression of oral carcinogenesis. *Clin Cancer Res*, 30(1):209-223. https://doi.org/10.1158/1078-0432.CCR-23-0318

Prgomet Z, Lindberg P, Andersson T, 2013. PP064: Wnt5a stimulates migration and invasion in OSCC. *Oral Oncol*, 49(suppl 1):S115-S116. https://doi.org/10.1016/j.oraloncology.2013.03.307

Prgomet Z, Andersson T, Lindberg P, 2017. Higher expression of WNT5A protein in oral squamous cell carcinoma compared with dysplasia and oral mucosa with a normal appearance. *Eur J Oral Sci*, 125(4):237-246. https://doi.org/10.1111/eos.12352

Prossomariti A, Piazzi G, Alquati C, et al., 2020. Are Wnt/β-catenin and PI3K/AKT/mTORC1 distinct pathways in colorectal cancer? *Cell Mol Gastroenterol Hepatol*, 10(3):491-506. https://doi.org/10.1016/j.jcmgh.2020.04.007

Purwaningsih NMS, Khor GH, Nik Mohd Rosdy NMM, et al., 2021. Wnt pathway in oral cancer: a review update. *Saudi Dent J*, 33(8):813-818. https://doi.org/10.1016/j.sdentj.2021.08.002

Ren Q, Chen JC, Liu YH, 2021. LRP5 and LRP6 in Wnt signaling: similarity and divergence. *Front Cell Dev Biol*, 9:670960. https://doi.org/10.3389/fcell.2021.670960

Reyes M, Flores T, Betancur D, et al., 2020. Wnt/β-catenin signaling in oral carcinogenesis. *Int J Mol Sci*, 21(13):4682. https://doi.org/10.3390/ijms21134682

Robert BM, Dakshinamoorthy M, Ganapathyagraharam Ramamoorthy B, et al., 2018. Predicting tumor sensitivity to chemotherapeutic drugs in oral squamous cell carcinoma patients. *Sci Rep*, 8:15545. https://doi.org/10.1038/s41598-018-33998-4

Roslan Z, Muhamad M, Selvaratnam L, et al., 2019. The roles of low-density lipoprotein receptor-related proteins 5, 6, and 8 in cancer: a review. *J Oncol*, 2019:4536302. https://doi.org/10.1155/2019/4536302

Sa P, Singh P, Panda S, et al., 2024. Reversal of cisplatin resistance in oral squamous cell carcinoma by piperlongumine loaded smart nanoparticles through inhibition of Hippo-YAP signaling pathway. *Transl Res*, 268:63-78. https://doi.org/10.1016/j.trsl.2024.03.004

Sajeev A, BharathwajChetty B, Vishwa R, et al., 2023. Crosstalk between non-coding RNAs and Wnt/β-catenin signaling in head and neck cancer: identification of novel biomarkers and therapeutic agents. *Non-coding RNA*, 9(5):63. https://doi.org/10.3390/ncrna9050063

Sakamoto T, Kawano S, Matsubara R, et al., 2017. Critical roles of Wnt5a–Ror2 signaling in aggressiveness of tongue squamous cell carcinoma and production of matrix metalloproteinase-2 via ΔNp63β-mediated epithelial-mesenchymal transition. *Oral Oncol*, 69:15-25. https://doi.org/10.1016/j.oraloncology.2017.03.019

Shen YH, Chen YL, Lin YT, et al., 2023. CDK5RAP2 is a Wnt target gene and promotes stemness and progression of oral squamous cell carcinoma. *Cell Death Dis*, 14(2):107. https://doi.org/10.1038/s41419-023-05652-z

Shiah SG, Shieh YS, Chang JY, 2015. The role of Wnt signaling in squamous cell carcinoma. *J Dent Res*, 95(2):129-134. https://doi.org/10.1177/0022034515613507

Silva JPN, Pinto B, Monteiro L, et al., 2023. Combination therapy as a promising way to fight oral cancer. *Pharmaceutics*, 15(6):1653. https://doi.org/10.3390/pharmaceutics15061653

Silveira FM, Schmidt TR, Neumann B, et al., 2023. Impact of photobiomodulation in a patient-derived xenograft model of oral squamous cell carcinoma. *Oral Dis*, 29(2):547-556. https://doi.org/10.1111/odi.13967

Smith AJ, Sompel KM, Elango A, et al., 2021. Non-coding RNA and frizzled receptors in cancer. *Front Mol Biosci*, 8:712546. https://doi.org/10.3389/fmolb.2021.712546

Sompel K, Elango A, Smith AJ, et al., 2021. Cancer chemoprevention through Frizzled receptors and EMT. *Discov Oncol*, 12:32. https://doi.org/10.1007/s12672-021-00429-2

Srivastava G, Matta A, Fu GD, et al., 2015. Anticancer activity of pyrithione zinc in oral cancer cells identified in small molecule screens and xenograft model: implications for oral cancer therapy. *Mol Oncol*, 9(8):1720-1735. https://doi.org/10.1016/j.molonc.2015.05.005

Sun LL, Kang XD, Wang C, et al., 2023. Single-cell and spatial dissection of precancerous lesions underlying the initiation process of oral squamous cell carcinoma. *Cell Discov*, 9:28. https://doi.org/10.1038/s41421-023-00532-4

Takabatake K, Kawai H, Omori H, et al., 2020. Impact of the stroma on the biological characteristics of the parenchyma in oral squamous cell carcinoma. *Int J Mol Sci*, 21(20):7714. https://doi.org/10.3390/ijms21207714

Takeshita A, Iwai S, Morita Y, et al., 2014. Wnt5b promotes the cell motility essential for metastasis of oral squamous cell carcinoma through active Cdc42 and RhoA. *Int J*

Oncol, 44(1):59-68.
https://doi.org/10.3892/ijo.2013.2172

Tan YH, Wang ZH, Xu MT, et al., 2023. Oral squamous cell carcinomas: state of the field and emerging directions. *Int J Oral Sci*, 15:44.
https://doi.org/10.1038/s41368-023-00249-w

Tasoulas J, Srivastava S, Xu XN, et al., 2023. Genetically engineered mouse models of head and neck cancers. *Oncogene*, 42(35):2593-2609.
https://doi.org/10.1038/s41388-023-02783-7

Tian JG, Cui XG, Feng YD, et al., 2018. Inhibition of WNT7A-β-catenin signaling pathway sensitizes oral squamous cell carcinoma to cisplatin. *Int J Clin Exp Pathol*, 11(10): 4926-4933.

Umar SA, Dong B, Nihal M, et al., 2022. Frizzled receptors in melanomagenesis: from molecular interactions to target identification. *Front Oncol*, 12:1096134.
https://doi.org/10.3389/fonc.2022.1096134

Urzì O, Gasparro R, Costanzo E, et al., 2023. Three-dimensional cell cultures: the bridge between in vitro and in vivo models. *Int J Mol Sci*, 24(15):12046.
https://doi.org/10.3390/ijms241512046

Vahle AK, Kerem A, Öztürk E, et al., 2012. Optimization of an orthotopic murine model of head and neck squamous cell carcinoma in fully immunocompetent mice – role of toll-like-receptor 4 expressed on host cells. *Cancer Lett*, 317(2): 199-206.
https://doi.org/10.1016/j.canlet.2011.11.027

Verrelle P, Gestraud P, Poyer F, et al., 2024. Integrated high-throughput screening and large-scale isobolographic analysis to accelerate the discovery of radiosensitizers with greater selectivity for cancer cells. *Int J Radiat Oncol Biol Phys*, 118(5):1294-1307.
https://doi.org/10.1016/j.ijrobp.2023.09.044

Vijayakumar G, Narwal A, Kamboj M, et al., 2020. Association of SOX2, OCT4 and WNT5A expression in oral epithelial dysplasia and oral squamous cell carcinoma: an immunohistochemical study. *Head Neck Pathol*, 14(3): 749-757.
https://doi.org/10.1007/s12105-019-01114-1

Walrath JC, Hawes JJ, van Dyke T, et al., 2010. Genetically engineered mouse models in cancer research. *Adv Cancer Res*, 106:113-164.
https://doi.org/10.1016/s0065-230x(10)06004-5

Wang YF, Cao Z, Liu FJ, et al., 2021. Clinical significance of activated Wnt/β-catenin signaling in apoptosis inhibition of oral cancer. *Open Life Sci*, 16(1):1045-1052.
https://doi.org/10.1515/biol-2021-0104

Wang ZM, Luo JQ, Xu LY, et al., 2018. Harnessing low-density lipoprotein receptor protein 6 (LRP6) genetic variation and Wnt signaling for innovative diagnostics in complex diseases. *Pharmacogenomics J*, 18(3):351-358.
https://doi.org/10.1038/tpj.2017.28

Wanigasekara J, Cullen PJ, Bourke P, et al., 2023. Advances in 3D culture systems for therapeutic discovery and development in brain cancer. *Drug Discov Today*, 28(2):103426.
https://doi.org/10.1016/j.drudis.2022.103426

Xie H, Ma YD, Li J, et al., 2020. WNT7A promotes EGF-induced migration of oral squamous cell carcinoma cells by activating β-catenin/MMP9-mediated signaling. *Front Pharmacol*, 11:98.
https://doi.org/10.3389/fphar.2020.00098

Xie J, Huang L, Lu YG, et al., 2021. Roles of the Wnt signaling pathway in head and neck squamous cell carcinoma. *Front Mol Biosci*, 7:590912.
https://doi.org/10.3389/fmolb.2020.590912

Xu F, Peng LL, Feng JY, et al., 2023. A prediction model of nodal metastasis in cN0 oral squamous cell carcinoma using metabolic and pathological variables. *Cancer Imaging*, 23:34.
https://doi.org/10.1186/s40644-023-00552-z

Yang WB, Zhang SH, Li TL, et al., 2023. Single-cell analysis reveals that cancer-associated fibroblasts stimulate oral squamous cell carcinoma invasion via the TGF-β/Smad pathway. *Acta Biochim Biophys Sin (Shanghai)*, 55(2): 262-273.
https://cstr.cn/32197.14.abbs.2022132

Yu FY, Yu CH, Li FF, et al., 2021. Wnt/β-catenin signaling in cancers and targeted therapies. *Signal Transduct Target Ther*, 6:307.
https://doi.org/10.1038/s41392-021-00701-5

Yuan Y, Xie XY, Jiang YC, et al., 2017. LRP6 is identified as a potential prognostic marker for oral squamous cell carcinoma via MALDI-IMS. *Cell Death Dis*, 8(9):e3035.
https://doi.org/10.1038/cddis.2017.433

Zanella ER, Grassi E, Trusolino L, 2022. Towards precision oncology with patient-derived xenografts. *Nat Rev Clin Oncol*, 19(11):719-732.
https://doi.org/10.1038/s41571-022-00682-6

Zeng CM, Chen Z, Fu L, 2018. Frizzled receptors as potential therapeutic targets in human cancers. *Int J Mol Sci*, 19(5): 1543.
https://doi.org/10.3390/ijms19051543

Zhang CP, Hao YL, Sun YY, et al., 2019. Quercetin suppresses the tumorigenesis of oral squamous cell carcinoma by regulating microRNA-22/WNT1/β-catenin axis. *J Pharmacol Sci*, 140(2):128-136.
https://doi.org/10.1016/j.jphs.2019.03.005

Zhang EJ, Li ZN, Xu ZF, et al., 2015. Frizzled2 mediates the migration and invasion of human oral squamous cell carcinoma cells through the regulation of the signal transducer and activator of transcription-3 signaling pathway. *Oncol Rep*, 34(6):3061-3067.
https://doi.org/10.3892/or.2015.4285

Zhang Y, Liu SH, Qu DW, et al., 2017. Kif4A mediate the accumulation and reeducation of THP-1 derived macrophages via regulation of CCL2-CCR2 expression in cross-talking with OSCC. *Sci Rep*, 7:2226.
https://doi.org/10.1038/s41598-017-02261-7

Zhang YH, Zhang YS, Niu WW, et al., 2021. Experimental study of almonertinib crossing the blood-brain barrier in EGFR-mutant *NSCLC* brain metastasis and spinal cord metastasis models. *Front Pharmacol*, 12:750031.
https://doi.org/10.3389/fphar.2021.750031

Zhang YL, Zu D, Chen Z, et al., 2020. An update on Wnt signaling pathway in cancer. *Transl Cancer Res*, 9(2):1246-1252. https://doi.org/10.21037/tcr.2019.12.50

Zhang YQ, Liu CX, Duan XL, et al., 2014. CREPT/RPRD1B, a recently identified novel protein highly expressed in tumors, enhances the β-catenin·TCF4 transcriptional activity in response to Wnt signaling. *J Biol Chem*, 289(33): 22589-22599. https://doi.org/10.1074/jbc.M114.560979

Zhao BR, Qin X, Fu R, et al., 2024. Supramolecular nanodrug targeting CDK4/6 overcomes BAG1 mediated cisplatin resistance in oral squamous cell carcinoma. *J Control Release*, 368:623-636. https://doi.org/10.1016/j.jconrel.2024.03.014

Zhong L, Liu YT, Wang K, et al., 2018. Biomarkers: paving stones on the road towards the personalized precision medicine for oral squamous cell carcinoma. *BMC Cancer*, 18:911. https://doi.org/10.1186/s12885-018-4806-7

Zhu EX, Li XM, Zhu L, et al., 2005. Expression of Wnt5a and β-catenin in Chinese oral squamous cell carcinoma of tongue. *J Hard Tissue Biol*, 14(2):247-248. https://doi.org/10.2485/jhtb.14.247