Cancer stem cells and their molecular signaling mechanisms in tongue squamous cell carcinoma (Review)

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Abstract. Tongue squamous cell carcinoma (TSCC) remains a significant clinical challenge, owing to its high prevalence and poor prognosis. Cancer stem cells (CSCs) serve a critical role in driving the initiation and progression of TSCC. The present review examined the unique characteristics and functional dynamics of CSCs in TSCC, with particular emphasis on the molecular signaling pathways that regulate their behavior. Key pathways, including Wnt/β-catenin, Notch and Hedgehog signaling pathways, are explored to provide a comprehensive understanding of the mechanisms underlying TSCC. The present study was reported in accordance with the Preferred Reported Items for Systematic Reviews. Articles were sourced from PubMed (pubmed.ncbi.nlm.nih.gov/) using the search terms 'tongue squamous cell carcinoma', 'cancer stem cells', 'molecular signaling', 'Wnt/β-catenin', 'Notch', 'Hotch' and 'Hedgehog', covering the period from January 2001 to October 2025. The review was limited to papers published in English. A total of 437 studies was retrieved. Excluding those studies are not closely related to the topic, 138 were reviewed in detail for their originality and relevance to the broader scope of the present review. By mapping these key signaling networks, the present review aimed to provide a strong foundation for the development of precision therapeutic strategies targeting TSCC.

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Abbreviations: Hh, Hedgehog; GLI, glioma-associated oncogene homolog; Ptch, patched; SMO, smoothened; APC, adenomatous polyposis coli; ADAMs, A disintegrin and metalloproteases; Notch, neurogenic locus notch homolog protein; NICD, Notch intracellular domain; Wnt, wingless-type MMTV integration site; Myc, MYC proto-oncogene; TCF, T cell factor; CD44, cluster of differentiation 44

Key words: tongue squamous cell carcinoma, cancer stem cells, molecular signaling, Wnt/β-catenin, Notch, Hh

Contents

1. Introduction

Tongue squamous cell carcinoma (TSCC) is a prevalent and aggressive malignancy of the head and neck region, associated with high morbidity and mortality rates, with an estimated global incidence of 151,000 new cases and 48,000 deaths annually as of 2023, yielding an age-standardized incidence rate of 1.7 per 100,000 and mortality of 0.54 per 100,000 (1). The pathogenesis of TSCC is multifactorial, driven by a complex interplay of genetic mutations, cumulative genetic alterations, signaling aberrations, epigenetic modifications, environmental exposures (such as tobacco use, alcohol consumption and human papillomavirus infection) and lifestyle-related risk factors (2).

In recent years, the concept of cancer stem cells (CSCs) has gained considerable attention as a key driver of tumor initiation, progression and therapeutic resistance. CSCs are a subpopulation of tumor cells with the capacity for self-renewal and differentiation into diverse cell types, thereby sustaining tumor growth and heterogeneity (3). TSCC CSCs exploit mitochondrial dynamics to reprogram lipid metabolism, promoting chemoresistance and survival under metabolic stress, while HPV+ TSCC subtypes exhibit distinct CSC properties that may be targeted for relapse-free therapy (4). These cells are sustained by specific molecular signaling pathways that are highly relevant in TSCC (5).

The present review aimed to elucidate the characteristics of CSCs in TSCC and the molecular signaling mechanisms that govern their function, with the ultimate aim of providing novel insights for future therapeutic strategies. A deeper understanding of the unique biology of CSCs in TSCC may facilitate the identification of new therapeutic targets and support the development of more effective treatments for this challenging disease.

2. Biological characteristics and significance of CSCs

CSCs are a subpopulation of tumor cells that possess the capacities for self-renewal and differentiation, which are essential for tumor initiation, maintenance and recurrence. They are often characterized by their ability to initiate tumor formation when transplanted into immunocompromised mice, a technique known as the xenograft assay (6,7). Additionally, CSCs can be identified by the expression of specific surface markers, such as CD44, CD24 and aldehyde dehydrogenase 1 (ALDH1), across various types of cancer, including TSCC (8). CD133 is also a recognized marker of CSCs across multiple malignancies and is often co-expressed with other stem cell markers (9); in ER-positive/HER2-negative breast cancer, high expression of CD133 is associated with a better chemotherapy response and survival rate (10).

In TSCC, $CD133^+$ cells exhibit stem cell-like properties and enhanced tumorigenic potential (11). Furthermore, a high density of α smooth muscle actin $(SMA)^+$ cancer-associated fibroblasts has been related to disease recurrence and poor survival, whereas the $CD133^+\alpha SMA^+$ phenotype appears to be mainly associated with vascular structures (12,13). Furthermore, the $CD44^+CD133^+$ cell subpopulation is regarded as a potential metastatic precursor, demonstrating increased proliferation, clonogenicity, invasion and migratory capacity (14).

Other approaches for identifying CSCs include functional assays, such as the sphere-forming assay, which evaluates the ability of cells to generate three-dimensional aggregates under non-adherent conditions, a feature indicative of stem-like properties (15). DNA methylation profiling has also been used to distinguish CSCs from non-CSCs. For example, A study has shown that, compared with non-CSCs, the promoter regions of specific tumor suppressor genes in CSCs are often hypermethylated, enabling clear differentiation between these cell populations. Furthermore, genetic and epigenetic profiling can be employed to distinguish CSCs from non-CSCs, providing deeper insight into the molecular mechanisms underlying their distinct characteristics (16).

Characteristics of TSCC-CSCs. In TSCC, CSCs exhibit several distinct biological characteristics that contribute to tumor progression and therapeutic resistance (6). A key feature of CSCs is their high capacity for self-renewal, which enables them to sustain the tumor cell population and drive continued growth (17). Additionally, TSCC-CSCs often display enhanced resistance to chemotherapy and radiotherapy, attributed to their ability to activate DNA repair pathways and evade apoptosis (18). These cells also exhibit a high degree of plasticity, with the ability to undergo epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition, thereby facilitating migration and invasion into surrounding tissues (19,20).

CSCs and EMT are considered to form a bidirectional reinforcing loop that promotes tumor progression (21). In one respect, the EMT process, activated by pathways such as TGF-β and Wnt, induces epithelial cells to lose polarity and acquire migratory and invasive capabilities through the action of key transcription factors (22). Concurrently, EMT confers stem-like properties by reprogramming differentiated tumor cells into CSCs, upregulating stem cell markers such as OCT4 and SOX2, and enhancing self-renewal capacity. Notably, CSCs promote EMT by secreting cytokines, including TGF-β and IL-6, thereby establishing a self-perpetuating cycle within the tumor microenvironment that drives surrounding cells toward a mesenchymal phenotype (23). Furthermore, TSCC-CSCs secrete various cytokines and growth factors that contribute to a supportive tumor microenvironment, promoting angiogenesis and immune evasion (24).

Microenvironment and epigenetic regulatory network. Hypoxia stabilizes HIF-1α, which activates stemness-associated genes and promotes metabolic reprogramming in CSCs, thereby enhancing self-renewal and chemoresistance. In TSCC, hypoxic niches also upregulate ATP-binding cassette (ABC) transporters, contributing to increased drug efflux (25). Extracellular matrix (ECM) components such as collagen, laminin and fibronectin interact with integrin receptors on CSCs to activate pro-survival signaling pathways (26). These interactions trigger focal adhesion kinase (FAK)/Src, PI3K/Akt and Ras/MAPK cascades, enhancing CSC self-renewal, inhibiting apoptosis and promoting EMT, thereby facilitating invasion and metastasis (27).

In TSCC, a stiffened ECM driven by the activation and transdifferentiation of cancer-associated fibroblasts (CAFs), which induces mechanotransduction via YAP/TAZ signaling, reinforces CSC plasticity and EMT (28). ECM-bound growth factors (TGF-β, EGF, HGF) maintain CSC quiescence and niche retention in TSCC via three mechanisms: Sequestration by ECM components, integrin-receptor crosstalk via FAK/Src and PI3K/Akt, and MMP-mediated activation (29).

In addition, epigenetic dysregulation, including DNA hypermethylation of tumor suppressor genes and histone modifications, suppresses differentiation-related genes while activating pathways such as Wnt/β-catenin and Notch (30).

Hepatocyte growth factor and its receptor c-MET serve important roles in tongue development and the carcinogenesis of head and neck squamous cell carcinoma (HNSCC) (31). Knockdown of c-MET reduces the sphere-forming ability and stem cell marker expression of HNSCC stem-like cells, while increasing sensitivity to cisplatin by decreasing the side population fraction and downregulating the ABCG2 transporter gene (31). Non-coding RNAs also contribute to the derepression of CSC-associated oncogenes. These ncRNAs form a regulatory triad that destabilizes tumor-suppressive checkpoints, enabling CSCs to maintain quiescence, evade therapy and initiate recurrence (32). The H19/miR-let-7/HMGA2 and miR-21/PTEN/STAT3 axes are particularly robust in TSCC, supported by clinical tissue analyses and TCGA-derived co-expression networks (33). In addition, hypoxia and ECM stiffness synergistically remodel the epigenetic landscape, maintaining CSCs in a stem-like state,with key therapeutic targets including HIF-1α inhibitors (e.g., PX-478 in Phase II

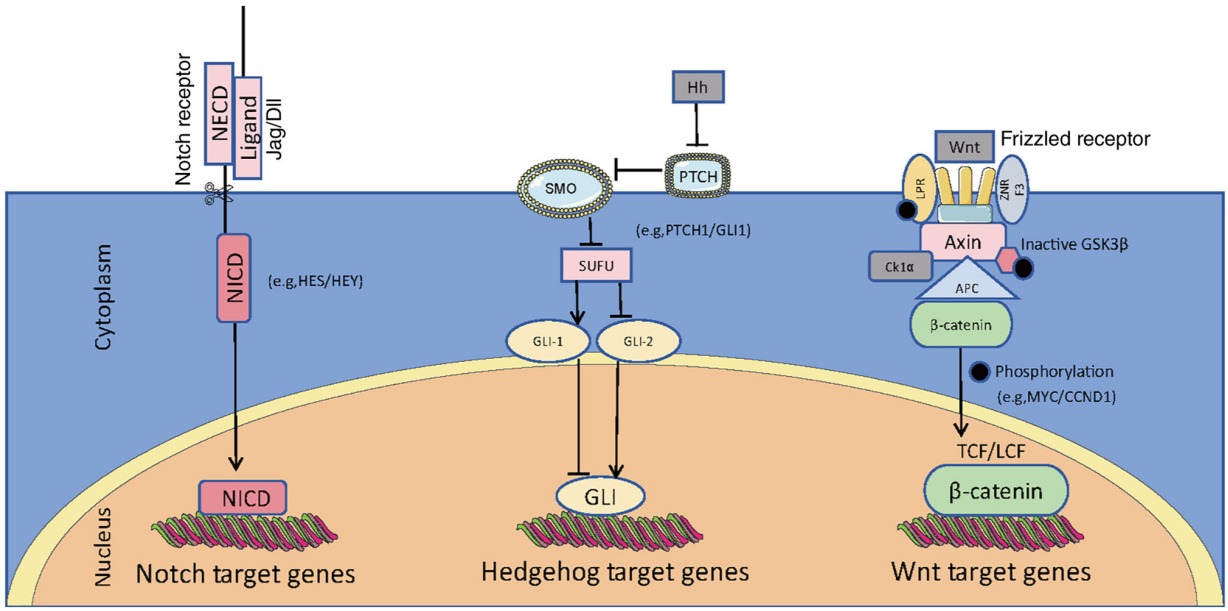

Figure 1. Simplified view of canonical Notch, Hh and Wnt signaling pathways in cancer. The Notch pathway involves ligand binding to receptors, releasing NICD into the nucleus to activate target genes like HES/HEY. The Hedgehog pathway activates GLI transcription factors via SMO. The Wnt pathway stabilizes β-catenin for nuclear translocation to regulate genes. Wnt ligands bind to Frizzled receptors, preventing β-catenin degradation and thus controlling cell proliferation and differentiation. NICD, Notch intracellular domain; NECD, Notch extracellular domain; Jag/DII, jagged/delta-like ligands; SMO, smoothened; PTCH, patched; Hh, Hedgehog; GLI, glioma-associated oncogene homolog; LPR, low-density lipoprotein receptor-related protein; Axin, axis inhibition protein; SUFU, suppressor of fused homolog; ZNRF3, zinc and ring finger 3; APC, adenomatous polyposis coli; TCF/LEF, T-cell factor/lymphoid enhancer factor; GSK3b, glycogen synthase kinase-3b; Ck1α, casein kinase 1α; HES, hairy and enhancer-of-split; HEY, HES related with YRPW motif; MYC, myelocytomatosis oncogene; CCND1, cyclin D1.

trials) and YAP/TAZ pathway modulators (e.g., Verteporfin, reducing CSCs by 60% in preclinical models) (34,35). Collectively, these mechanisms support CSC resilience and present potential targets for combination therapies in TSCC (36). The clinical significance of CSCs in TSCC is substantial, as these cells are implicated in several key aspects of cancer biology that directly affect patient outcomes (37). CSCs serve a key role in tumor recurrence and metastasis (38); owing to their resistance to conventional therapies, CSCs can survive treatment and subsequently drive tumor regrowth, contributing to poor prognosis (37). Additionally, the presence of CSCs in TSCC is associated with an increased likelihood of metastasis, as these cells possess the capacity to migrate and colonize distant sites (39). Therefore, the identification and targeting of CSCs in TSCC represents a promising strategy for improving therapeutic efficacy and patient survival (40). Furthermore, a deeper understanding of the molecular and cellular mechanisms underlying CSCs in TSCC may facilitate the development of novel targeted therapies capable of overcoming current treatment limitations (41,42).

3. Roles of the Wnt/β-catenin signaling pathway in TSCC

The Wnt/β-catenin signaling pathway is a key regulator of cell proliferation, differentiation and apoptosis (43). In the absence of Wnt ligands, β-catenin is phosphorylated by a destruction complex composed of proteins such as axis inhibition protein, adenomatous polyposis coli (APC) and glycogen synthase kinase-3b, which targets it for proteasomal degradation (44). However, when Wnt ligands bind to Frizzled receptors and low-density lipoprotein-related proteins 5 and 6 co-receptors, this phosphorylation is inhibited, allowing β-catenin to accumulate in the cytoplasm and subsequently translocate into the nucleus (45). In the nucleus, β-catenin interacts with T cell factor (TCF)/lymphoid enhancer factor family (LEF) transcription factors to activate the expression of target genes involved in cell proliferation and survival (Fig. 1) (46,47). In healthy cells, this destruction complex tightly regulates cytoplasmic β-catenin levels. Aberrant activation of the pathway can occur through mutations in CTNNB1 (encoding β-catenin) or APC, epigenetic silencing of pathway inhibitors such as secreted frizzled-related proteins and Dickkopf proteins, or autocrine/paracrine upregulation of Wnt ligands (48). This hyperactivation leads to β-catenin accumulation and its translocation into the nucleus. Within the nucleus, β-catenin forms complexes with TCF/LEF transcription factors, driving the expression of oncogenic target genes (49). These genes regulate key cancer hallmarks in TSCC, including uncontrolled proliferation (via c-Myc and Cyclin D1), evasion of apoptosis, EMT (which in turn facilitates invasion and metastasis), maintenance of CSCs and angiogenesis (50). The Wnt/β-catenin signaling pathway molecular mechanism is highly conserved across species and serves a critical role in both normal developmental processes and disease pathogenesis, including TSCC (51).

The Wnt/β-catenin signaling pathway has been implicated in the maintenance and expansion of CSCs in TSCC (52). Accumulating evidence suggests that activation of this pathway promotes the expression of stemness-associated genes, such as SOX2 and OCT4, which are essential for maintaining CSC properties (53,54). Therefore, targeting the Wnt/β-catenin signaling pathway in TSCC may represent a promising strategy for eliminating CSCs and improving patient outcomes (55).

4. Roles of the Hedgehog (Hh) signaling pathway in TSCC

The Hh signaling pathway is a key regulator of cell growth and differentiation during embryonic development and in adult tissues (56). The pathway is initiated when Hh ligands bind to the Patched (Ptch) receptor, relieving its inhibition of the Smoothened (Smo) protein (57). Activation of Smo promotes the translocation of glioma-associated oncogene homolog (GLI) transcription factors from the cytoplasm to the nucleus, where they drive the transcription of Hh target genes (58,59). The pathway is tightly regulated by several proteins, including Suppressor of Fused, which negatively regulates Gli activity, and Costal-2 (Cos2), which helps stabilize GLI proteins in the cytoplasm (Fig. 1) (60,61). Dysregulation of Hh signaling has been implicated in various types of cancer, including TSCC, where it contributes to tumor progression and maintenance (62).

In TSCC, the Hh signaling pathway is frequently aberrantly activated, contributing to disease pathogenesis and progression (63). This activation may occur through multiple mechanisms, including upregulation of Hh ligands, mutations in the Ptch receptor or alterations in other regulatory components of the pathway (64). For example, mutations in the Ptch gene can result in constitutive pathway activation even in the absence of ligand binding (65,66). In addition, the expression levels of Hh target genes, such as GLI1 and GLI2, are often upregulated in TSCC, indicating sustained pathway activity (67,68). This persistent activation promotes cell proliferation, inhibits apoptosis and enhances cancer cell survival, thereby contributing to the aggressive behavior of TSCC (69).

The Hh signaling pathway has been shown to serve a critical role in the maintenance and expansion of CSCs in TSCC (70), by upregulating stem cell markers and genes involved in cell cycle regulation (71). For example, the transcription factor GLI1, a key mediator of Hh signaling, enhances the expression of Nanog and OCT4, which are essential for maintaining CSC stemness (72,73). Furthermore, Hh signaling also increases the expression of ABC transporters, which contributes to CSC drug resistance (74). Thus, targeting the Hh pathway may represent a promising therapeutic strategy for eliminating CSCs and improving the prognosis of patients with TSCC (75).

5. Roles of the Notch signaling pathway in TSCC

Notch signaling mediates short-range cell-to-cell communication through interactions between ligands and receptors on adjacent cells. When a Notch ligand binds to its receptor, it triggers cleavage at the S2 site by ADAM10 and ADAM17, resulting in shedding of the extracellular domain (76). This is followed by γ-secretase-mediated cleavage at the S3 site within the transmembrane region. After S3 cleavage, the Notch intracellular domain (NICD) is released from the plasma membrane and translocates to the nucleus (77). In the nucleus, NICD interacts with recombination signal binding protein for immunoglobulin κ J region, also known as CBF1/Suppressor of Hairless/Lag-1 (CSL), converting the transcriptional repressor complex into a transcriptional activator complex and thereby promoting the expression of Notch target genes (78).

The Notch signaling pathway is a highly conserved intercellular communication system that plays a critical role in cell fate determination, differentiation, and proliferation (79). It involves a family of transmembrane receptors (Notch1-4) that are activated upon binding to ligands such as Jagged and Delta-like proteins (80). Following ligand engagement, the Notch receptor undergoes two successive proteolytic cleavages, resulting in the release of the NICD, which translocates to the nucleus (81). In the nucleus, NICD interacts with the DNA-binding protein CSL, displacing co-repressors and recruiting co-activators to initiate transcription of target genes (82). This tightly regulated mechanism ensures precise control of multiple cellular processes, making Notch signaling essential for tissue homeostasis and developmental regulation (83).

In TSCC, Notch signaling is frequently upregulated and serves a significant role in tumor progression and maintenance (84). Activation of the pathway is often driven by upregulation of ligands such as Jagged1 and delta-like ligand 1, which promote tumor cell proliferation and survival (Fig. 1). In addition, mutations or amplifications in Notch receptors can lead to constitutive pathway activation, further contributing to oncogenic transformation (85). In HNSCC (including TSCC), inactivation mutations of NOTCH1 are more common, but amplification (such as an increase in copy number) of NOTCH3 can lead to excessive activation of the pathway, promoting tumor invasion (86).

The regulatory mechanisms of Notch signaling in TSCC are complex and involve both positive and negative feedback loops, as well as crosstalk with other pathways. The Wnt signal upregulates the expression of the Jagged1 ligand, further activating Notch, and Akt directly phosphorylates Notch1, enhancing its transcriptional activity (87). Notch can activate NF-κB, maintaining the inflammatory microenvironment by upregulating IL-6 and IL-8, enhancing the invasiveness of tumors; furthermore, the intracellular segment of Notch1 (NICD) can directly bind to YAP/TAZ, inhibiting the tumor suppressive effect of the Hippo pathway and promoting the characteristics of tumor stem cells (88,89). These interactions create a dynamic regulatory network that can either enhance or suppress Notch activity, depending on the tumor microenvironment and specific genetic context (84).

Notch signaling has been implicated in the maintenance and expansion of CSCs in TSCC (90). It promotes CSC properties by activating transcriptional programs that enhance stemness, including the expression of OCT4, SOX2 and NANOG (91). In addition, Notch signaling can suppress differentiation pathways, thereby preserving the undifferentiated state of CSCs (17). The role of Notch in CSCs extends beyond transcriptional regulation; it also influences cell cycle progression, apoptosis and EMT, all of which are critical for CSC survival and metastatic potential (92,93). Therefore, targeting Notch signaling represents a potential therapeutic strategy to deplete CSCs and potentially improve outcomes in TSCC (54).

6. Interactions among multiple signaling pathways and their significance in TSCC

CSCs dynamically interact with key signaling pathways to drive tumorigenesis and therapeutic resistance. In TSCC, activation of the Wnt/β-catenin pathway stabilizes nuclear β-catenin in $CD44^+$ CSCs, leading to the upregulation of c-MYC and OCT4 and sustaining self-renewal and chemoresistance (94).

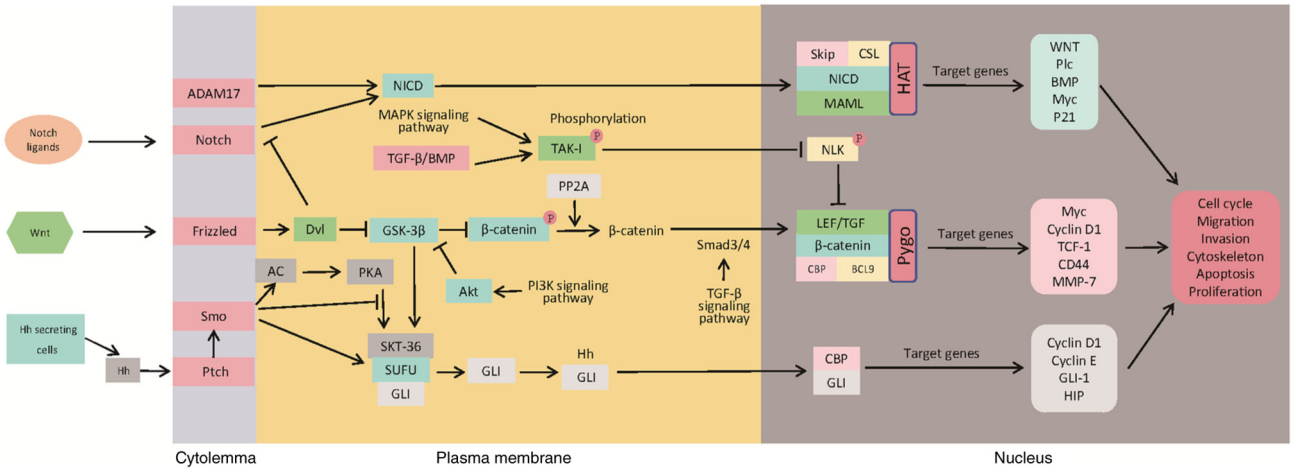

Figure 2. Crosstalk between Notch, Wnt and Hh signaling pathways in cancer. They coordinate cellular functions through receptor-ligand binding, intracellular signal cascades, nuclear translocation of effector proteins to regulate gene expression, and feedback loops. ADAM17, a disintegrin and metalloproteinase 17; SMO, smoothened; Ptch, patched; NICD, Notch intracellular domain; BMP, bone morphogenetic protein; Dvl, dishevelled; AC, adenylate cyclase; PKA, protein kinase A; SUFU, suppressor of fused homolog; GLI, glioma-associated oncogene homolog; Hh, hedgehog; TAK1, transforming growth factor-β-activated kinase 1; PP2A, protein phosphatase 2A; SKIP, SKI-interacting protein; CSL, CBF1/Su(H)/Lag-1; CBP, CREB-binding protein; BCL9, B-cell lymphoma 9; LEF, lymphoid enhancer factor; HAT, histone acetyltransferase; TCF, T-cell factor; HIP, Hh-interacting protein; MAPK, mitogen-activated protein kinase; GSK-3, glycogen synthase kinase-3; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; Smad, mothers against decapentaplegic homolog; TGF, transforming growth factor; MAML, mastermind-like; Pygo, pygopus; NLK, nemo-like kinase.

Notch signaling, through NICD cleavage, induces EMT by promoting HES1 expression, thereby facilitating metastasis (95). Hh pathway activation enhances CSC proliferation and contributes to post-therapy recurrence (96). Concurrently, PI3K/Akt/mTOR pathway alterations reprogram CSC metabolism under hypoxic conditions, while NF-κB activation driven by chronic inflammation suppresses apoptotic signaling. These pathways engage in extensive crosstalk; for example, tumor microenvironment-derived TGF-β amplifies Wnt and Notch signaling, thereby locking CSCs into a drug-tolerant state (97). Targeting these signaling hubs can disrupt CSC-driven progression, as demonstrated in TSCC xenograft models where Wnt inhibition reduced tumor-initiating capacity by ~70% (98). Collectively, these findings underscore the therapeutic potential of pathway-specific targeting for CSC depletion in TSCC.

The interaction between multiple signaling pathways is a complex yet critical aspect of cellular regulation, particularly in TSCC (99). These pathways often converge and crosstalk to regulate key cellular processes such as proliferation, survival and differentiation (100). For example, the PI3K/Akt pathway, which is frequently activated in cancer, can interact with the MAPK/ERK pathway to enhance cell survival and proliferation (100,101). This interaction may occur through shared downstream effectors or crosstalk at the level of upstream receptors (102). In addition, the NF-κB pathway, which is well known for its role in inflammation and stress responses, integrates signals from multiple pathways, including those activated by growth factors and cytokines, to regulate gene expression and cellular fate (103). Understanding these mechanisms is essential for the development of targeted therapies aimed at disrupting these interactions and inhibiting cancer progression.

The synergistic effects of multiple signaling pathways in TSCC are profound and multifaceted. When concurrently activated, these pathways can exert a stronger influence on cancer cell behavior than when activated individually (101). For example, co-activation of the PI3K/Akt and MAPK/ERK pathways enhances cell proliferation and resistance to apoptosis, contributing to the aggressive nature of TSCC (104,105); interactions between these pathways can also promote EMT, a process closely associated with metastasis (106). Additionally, EMT is driven by the coordinated activity of pathways such as TGF-β and Wnt/β-catenin, which may be further amplified through crosstalk with additional signaling networks (Fig. 2) (107,108). In TSCC and HNSCC, the co-activation of the PI3K/AKT and MAPK/ERK pathways significantly enhances tumor proliferation, anti-apoptosis and the EMT process (109). This synergistic activation not only drives malignant transformation but also contributes to therapeutic resistance, making TSCC particularly challenging to treat (110).

The interactions between multiple signaling pathways also have a significant impact on CSCs, which are considered key drivers of tumor initiation, progression and recurrence in TSCC (3). CSCs exhibit a distinct signaling landscape compared with non-stem cancer cells (17). For example, the Notch and Wnt/β-catenin pathways are frequently upregulated in CSCs and serve critical roles in maintaining stemness and self-renewal capacity (93). These pathways interact with additional signaling networks, such as PI3K/Akt and MAPK/ERK, to establish a robust signaling environment that supports CSC survival and proliferation (111). Disrupting these interactions could potentially reduce the CSC population and thereby inhibit tumor growth and metastasis (112). Because CSCs drive tumor initiation, growth, therapy resistance, recurrence and metastasis, reducing their abundance may suppress primary tumor progression and the formation of secondary metastatic lesions (113,114), thus targeting a fundamental source of malignancy and relapse. Therefore, utilizing the crosstalk between these signaling pathways to develop therapeutic targets against TSCC may represent a promising strategy in the future (115).

7. Therapeutic challenges of CSCs in TSCC

CSCs in TSCC exhibit marked resistance to conventional chemotherapy and radiotherapy, thus posing significant challenges to effective treatment, while also offering opportunities for the development of novel treatment strategies (116). A study has shown that TSCC-CSCs express specific biomarkers, including ALDH, CD44, NANOG, OCT4 and BMI1. These markers not only facilitate the identification of CSCs, but may also serve as potential therapeutic targets (117).

Complexity of molecular heterogeneity. CSCs in TSCC exhibit significant molecular heterogeneity. CSCs derived from different patients, and even within the same tumor, may display distinct molecular profiles and patterns of signaling pathway activation (99). This heterogeneity complicates the development of a unified targeted therapeutic strategy against CSCs. For example, upregulated of the ZFX gene has been associated with tumor progression in certain TSCC cases; however, its expression levels and functional roles vary considerably among patients (118).

Redundancy and compensatory mechanisms of signaling pathways. CSCs typically rely on multiple signaling pathways to maintain their stemness and viability, including the Wnt/β-catenin, Notch, Hh and HIF-1α/MCT4 pathways (119). When one pathway is inhibited, others may become activated to compensate for the loss of function, thereby contributing to treatment resistance. For example, in colon cancer, after inhibiting the Wnt pathway, the Hh pathway will in a compensatory manner activate, maintaining the CSC characteristics by upregulating GLI1 (120). In glioblastoma, blocking the Notch signal will lead to an increase in HIF-1α expression, and through glycolytic reprogramming, it will support the survival of CSCs (121). However, this multi-target mechanism may encounter complex regulatory challenges in clinical applications (122). For instance, in pancreatic cancer, when both the Wnt and Hh pathways are simultaneously inhibited, NF-κB will undergo compensatory activation, which instead accelerates metastasis (123).

Rapid evolution of treatment resistance. CSCs exhibit a high degree of genomic instability and adaptability, enabling them to rapidly develop resistance mechanisms under therapeutic pressure (124). For example, during chemotherapy, CSCs may evade treatment by upregulating drug efflux pumps such as ABC transporters, enhancing DNA repair capacity or reprogramming cellular metabolic pathways (125). CSCs evade therapy through three interconnected mechanisms: Overexpression of ABC transporters (e.g., ABCB1/P-gp and ABCG2) actively expels chemotherapeutics like paclitaxel and doxorubicin, reducing intracellular drug concentrations; upregulation of DNA repair proteins (RAD51, ERCC1, PARP1) enables efficient repair of radiation- and alkylator-induced DNA double-strand breaks, suppressing apoptosis; and dynamic metabolic reprogramming-shifting between glycolysis and oxidative phosphorylation while upregulating MCT4 and GLUT1-maintains low ROS levels and adapts to hypoxic, acidic microenvironments (126).

Barriers to clinical translation. Translating laboratory findings on CSCs into clinical practice presents several challenges. The proportion of CSCs within tumors is typically very low (for example, $ALDH^+$ cells account for only 1.3% of the Tca8113 cell line), requiring highly specific therapeutic approaches to effectively target these cells (127). CSCs impede clinical translation because of their hypoxic microenvironment, drug resistance and heterogeneity; low abundance and missing biomarkers hinder trials, and current models fail to mimic human biology; they avoid immunity via PD-L1 and Tregs, sustain stemness via methionine metabolism and lack validated biomarkers without consensus on endpoints (128,129). Additionally, there is a lack of reliable *in vivo* models that accurately recapitulate the biological behavior and treatment responses of CSCs in TSCC.

8. Conclusion

The present review of CSC characteristics in TSCC and key signaling pathways such as Wnt/β-catenin, Notch and Hh aimed to advance the understanding of TSCC pathogenesis (130). These findings highlight the critical role of CSCs in TSCC initiation and progression, providing a theoretical basis for the development of targeted therapies against CSCs and their regulatory networks (8). A balanced interpretation of existing research is essential; while a study emphasized the role of Wnt/β-catenin in CSC maintenance, others highlight the synergistic effects of Notch and Hh signaling (108). CSCs resist therapy by leveraging Wnt/β-catenin for self-renewal, while Notch and Hh signaling synergistically enhance survival and immune evasion (131). In pancreatic cancer models where dual inhibition of Notch and Hh reduced CSC frequency by 70% compared to single-pathway targeting (132).

It could be considered that simultaneous targeting of multiple pathways may be more effective in eliminating CSCs and preventing recurrence (133). Integrating molecular insights with clinical data is crucial for translating these findings into practical therapies (134). Future research should further elucidate pathway mechanisms and interactions to support the development of personalized medicine approaches (135), potentially leading to more effective, less toxic treatments for TSCC and improved patient outcomes (75). Overall, the exploration of CSCs in TSCC holds promise for transforming current cancer treatment strategies (136). Bridging laboratory findings with clinical application will be essential for the development of targeted therapies that improve prognosis and quality of life for patients (137).

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Authors' contributions

XZ and WC designed the present study. XG, WR and QZ prepared the first draft. WR prepared the figures. CM and XG

reviewed and edited the manuscript. Data authentication is not applicable. All authors were involved in revising the paper and had full access to the data. All authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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