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Review Article

Cancer stem cells of head and neck squamous cell carcinoma; distance towards clinical application; a systematic review of literature

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Abstract: Head and neck squamous cell carcinoma (HNSCC) is the major pathological type of head and neck cancer (HNC). The disease ranks sixth among the most common malignancies worldwide, with an increasing incidence rate yearly. Despite the development of therapy, the prognosis of HNSCC remains unsatisfactory, which may be attributed to the resistance to traditional radio-chemotherapy, relapse, and metastasis. To improve the diagnosis and treatment, the targeted therapy for HNSCC may be successful as that for some other tumors. Nanocarriers are the most effective system to deliver the anti-cancerous agent at the site of interest using passive or active targeting approaches. The system enhances the drug concentration in HCN target cells, increases retention, and reduces toxicity to normal cells. Among the different techniques in nanotechnology, quantum dots (QDs) possess multiple fluorescent colors emissions under single-source excitation and size-tunable light emission. Dendrimers are the most attractive nanocarriers, which possess the desired properties of drug retention, release, unaffecting by the immune system, blood circulation time enhancing, and cells or organs specific targeting properties. In this review, we have discussed the up-to-date knowledge of the Cancer Stem Cells of Head and Neck Squamous Cell Carcinoma. Although a lot of data is available, still much more efforts remain to be made to improve the treatment of HNSCC.

Keywords: Cancer stem cells, head neck squamous cell carcinoma, target therapy, nanotechnology, quantum dots

Introduction

Head and neck cancer (HNC) is the malignancy arising from the epithelium of the upper digestive tract and upper respiratory tract, including the nasal cavity, paranasal sinus, pharynx, oral cavity, larynx, and cervical esophagus [1], as shown in **Figure 1**. Head and neck squamous cell carcinoma (HNSCC) are the major pathological type of HNC [2, 3]. Only 40-50% of people with HNSCC live for five years after being diagnosed [4]. The main causes of HNSCC are exposure to alcohol, betel quid products, and tobacco; where the risk factors include carcinogens, tobacco smoking, alcohol, human papillomavirus (HPV) infection, and genetic predisposition [5-7]. The major issue in HNSCC pathogenesis is carcinomas development in mucosal epithelium preneoplastic fields which are made up of genetically altered cells and clonally similar to carcinoma [8]. On the tumours excised state, it may extend into the surgical margins, causing second primary tumors. The dissemination of HNSCC occurs in lymph nodes in the neck region. Here, the unravelling of molecular and biological process of HNSCC may be useful for better management and development of personalized therapies [9, 10]. The disease ranks the sixth most common malignancy worldwide, with an increasing incidence rate yearly [11]. Squamous cell carcinoma (SCC) accounts for over 90% of all head and neck malignancies [12, 13]. Despite various interdisciplinary therapy, HNSCC treatment is ineffective [14-16]. The theory of cancer stem cells (CSCs) is one of the milestones of cancer therapy. According to this theory, CSCs are a small subpopulation of tumor bulk with the abilities of self-renewal and differentiation into secondary heterotypic groups [17].

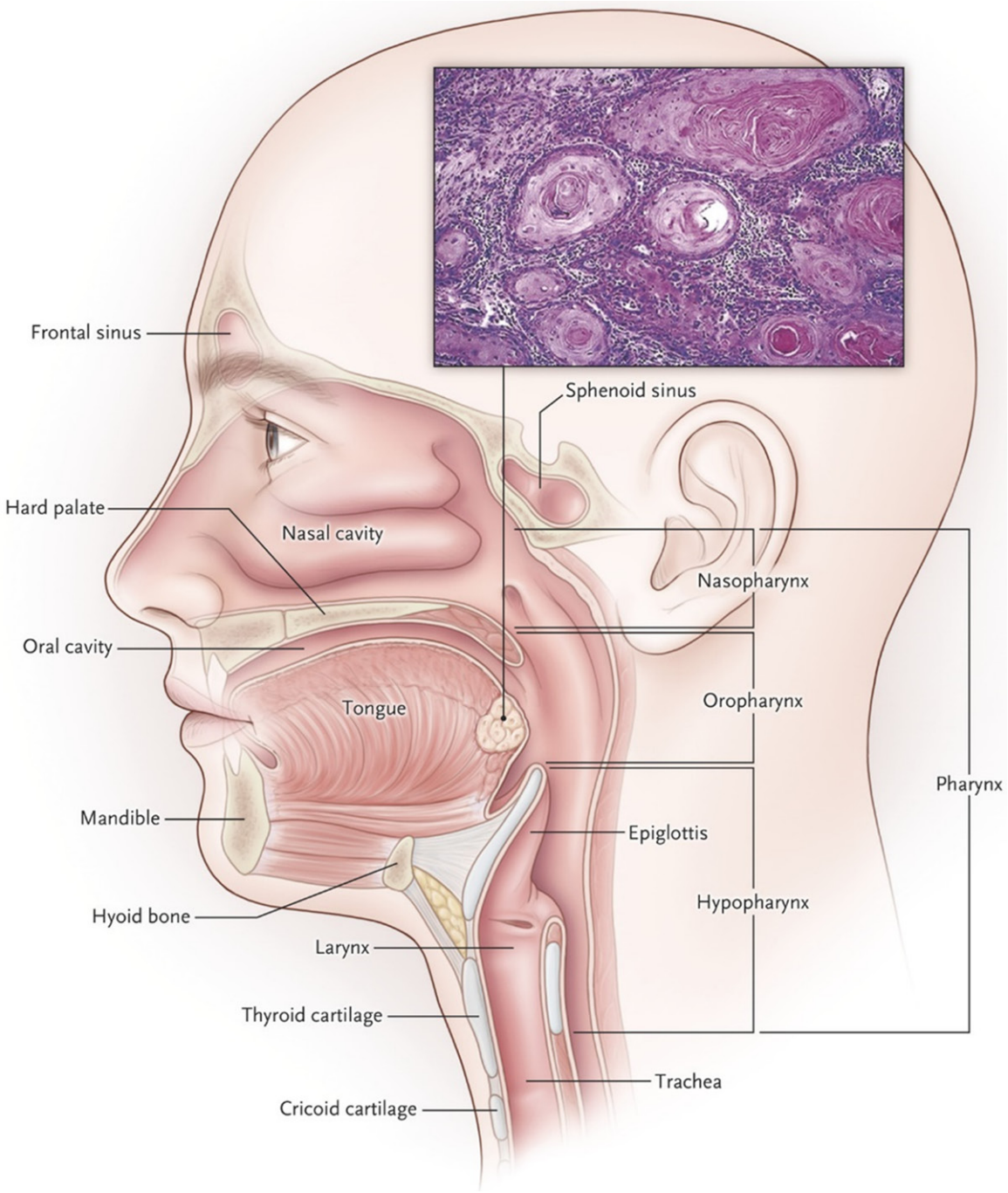

Figure 1. Major anatomical sites of HNSCC. Organs involved in HNC are the nasal cavity, paranasal sinus, pharynx, oral cavity, larynx, and cervical esophagus. With permission from Chow, 2020.

Eliminating CSCs may help to cure cancer. The Stemness Phenotype Model proposed a model and stated that CSCs have no specific subpopulation of tumors and cancer cells possess plasticity in CSCs and non-CSCs stemness that can interconvert into each other in different microenvironments. This model predicts a pure CSC phenotype cancer cell to pure non-CSC [18-20]. The dissemination from primary tumors and seeding of new tumors from other distant body places involves an invasion-metastasis cascade. Carcinoma dissemination may occur by two mechanisms - single cell dissemination and collective dissemination of

tumor clusters. CSCs are believed to be the origin of a tumor and the source of metastasis. CSCs have more substantial potential for stemness, epithelial-to-mesenchymal transition (EMT), therapeutic resistance, and immune escape [21, 22]. Cancer-associated fibroblasts (CAFs) are major components of their microenvironment, performing numerous functions including remodeling, matrix deposition, signaling, and crosstalk with host immunity [23]. New markers and their molecular interactions may be identified for more tailored cancer therapies. Post-therapy relapse may be attributed to inadequate elimination of CSCs [24]. The stem-like cells have been isolated and identified from most solid tumors, including HNSCC. The cluster of differentiation (CD) molecules including CD44, CD133, and ALDH (Aldehyde dehydrogenase) have been identified as specific markers of CSCs in HNSCC. Side population (SP) cells and cells with the ability of sphere formation in a medium contained in EGF are also identified as stem-like cells of HNSCC [25]. The PI3K pathway in HNSCC shows significant activating genetic events which may be useful for further studies [26]. This will also unravel the molecular events behind it. In molecular biology, HNC is a manyfold complex process proceeding from carcinogen causing a single mutation to the dysregulation of many metabolic processes in signaling pathways where these events occur in different conditions and states. The molecular biology of HNS still needs much work to be recognized at every step and stage for a better understanding [27]. Many signaling pathways have been identified involved in HNC which may be a potential target and also inhibition of epidermal growth factor receptor (EGFR) for therapeutic strategy is one of the key targets.

The HNSCC microenvironment is permissive and seems more aggressive in nature, and the response to tumour stress and hypoxia by the immune system are still needed to be explored. Solving these phenomena may increase our knowledge of molecular biology for better management of HNSCC in future.

Potential regulators of HNSCC CSCs: potential targets and current bottleneck

We searched PUBMED's literature on HNSCC and CSCs and collected data from CSCs regulators (Tables S1, S2 and S3). These regulators include: Phosphoinositide 3 kinase (PI3K) [28], mTOR signaling pathway [29], Hyaluronan (HA) [30], Snail [31], Human papillomavirus type 16 (HPV16) [32], Maternal embryonic leucine zipper kinase (MELK) [33], Renin-angiotensin system (RAS) [34], Short palate, lung and nasal epithelium clone 1 (SPLUNC1) and Mixed lineage leukemia-3 (MLL3) [35], X-linked inhibitor of apoptosis protein (XIAP) [36], Moloney murine leukemia virus insertion site 1 (BMI1) [37], Mitogen-activated protein kinases (p38 MAPK) [38], Wingless/Integrated (Wnt)/β-catenin [39], Sry-like high-mobility group box (SOX8) [40], Sry-like high-mobility group box (SOX2) [41], mitotic arrest deficient 1 (RARS-MAD1L1) [42], LIN28 proteins [43], heat shock protein 90 (HSP90) [44], 5T4 (an *N*-glycosylated transmembrane protein whose gene is found on chromosome 6q14-15) [45], c-Met (a proto-oncogene) [46, 47], metastasis-associated colon cancer-1 (MACC1) [48], The Hippo-TAZ [49], Oct-4 [50], RXRα [51], epidermal growth factor receptor (EGFR) [52, 53], Notch1 [54, 55], Disruptor of telomeric silencing 1 (DOT1L) [56], Nucleotide-binding domain (NOD)-like receptor protein 3 inflammasome (NLRP3) [57], Tumor necrosis factor receptor-associated factor 6 (TRAF6) [58], glucose-regulated protein 78 (GRP78) [59], S100 Calcium Binding Protein A4 (S100A4) [60], RhoC (a member Rho family of GTPases) [61], Glycogen synthase kinase-3 beta (GSK3β) [62], c-Fos (a proto-oncogene) [63], G9a (also called EHMT2 or KMT1C, is a major euchromatic methyltransferase) [64], histone deacetylase (HDAC) [65], Senescence-associated secretory phenotype (SASP) [66], PinX1 (a potent telomerase regulator) [67], Sialyl Lewis X (sLeX) [68], fucosylation [69], CD200 [70], casein kinase 2 (CK2, a constitutively active Ser/Thr protein kinase) [71], CD10 [72], SDF-1a/CXCR4 (Stromal cell-derived factor-1) [73], Smad ubiquitination regulatory factor (SMURF1) [74], Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2) [75], GLI family zinc finger 3 (GLI3); a mediator of genetic diseases [76], Zinc finger E-box binding homeobox 1 (ZEB1/ZEB2) [77], Inhibitor of binding/differentiation 2 (Id2) [78], Bone morphogenetic protein 4 (BMP4) [79], Interferon-stimulated gene 15 (ISG15) [80], ecotropic viral integration site 1 (EVI1) [81], Signal transducer and activator of transcription 3 (STAT3) [82], S-phase kinase associated protein 2 (Skp2) [83], Latent membrane protein 2A (LMP2A)

[84], Olfactomedin-4 (OLFM4) [85], topoisomerases [86], JARID1B (also known as PLU-1, is a Retinoblastoma-Binding Protein 2 (RBP2) Homolog, and a member of the jumonji, AT rich interactive domain (JARID) family with H3K4 demethylase activity) [87], Slug (an epithelial mesenchymal transition master gene) [88], CC-chemokine receptors (CCL21/CCR7) [89], Metastasis-associated Protein 3 (MTA3) [90], CMTM6 (belongs to the CKLF-like MARVEL transmembrane domain-containing family; CMTM1-8) [91], phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK-3CA) [92], Secreted Frizzled-related Protein 1 (SFRP1) [93], Nuclear factor-erythroid factor 2-related factor 2 (Nrf2) [94], Glioma-associated oncogene homologue 1 (Glia1) [95], Cd47-Signal Regulatory Protein α (CD47-SIRPα) [96], Wolf-Hirschhorn syndrome candidate 1 (WHSC1) [97], Zinc finger and SCAN domain containing 4 (ZSCAN4) [98], cystine transporter (xCT) [99], Mediator Complex Subunit 28 (RCOR1/MED28) [100], Wnt Family Member 5A (WNT5A) [101], the estrogen-regulated anterior gradient 2 (AGR2) [102], Cathepsins [103], cytochrome (CYP1B1) [104], signaling promotes regenerative proliferation (VAV2) [105], Tetraspanin 1 (TSPAN1) [106], Tropomyosin-related tyrosine kinase B (TrkB) [107], phosphoglycerate kinase (PGK1) [108], insulin-like growth factor 1 (IGF-1) [109], super-enhancers (SEs) [110], HOXA10-AS (a regulator of homeobox A10) [111], hydroxysteroid 17-β dehydrogenase 7, hydroxysteroid 17-β dehydrogenase 7 (HSD17B7) [112], Prostaglandin E_2 [113]. Aberrant miRNAs (lower level) miR-204 [114], miR-34a [115], microRNA-200c [116], MiR-520b [117], microRNA let-7a [118], Let-7c [119], miR-34a [120] and Longnoncoding RNA-Pvt1 (LncRNA-Pvt1) [121], Long intergenic non-protein coding RNA, p53 induced transcript (LINC-PINT) [122], Hematopoietic cell-specific Lyn substrate-associated protein X-1 (miR-125a/HAX-1) [123], LINC00963 [124], miR-495 (low) [125], CCNG2 (miR-1246/CCNG2) [126] could regulate HNSCC CSCs. The niche associated factors; hypoxia [127], interleukin-6 (IL-6) [128], IL-4 [129], IL-1β [130], EGF [131], TGF-β [132], tumor associated markers (TAM) markers [133], cancer-associated fibroblast [134] also promote the stemness of HNSCC CSCs. In addition, chewing tobacco [135], arecoline-exposure [136], nicotine [137], and cigarette smoke [138] could induce and activate malignant phenotypes and stemness. It may suggest that HNSCC patients need a lifelong ban on tobacco and arecoline.

From data (Tables S1, S2 and S3), we have summarized the following two basic pieces of information 1). Most studies used HNSCC cell lines or available squamous cell carcinoma cell lines of a particular organ as in vitro research subjects; 2). Most studies have applied CSCs markers (CD44, ALDH, CD133), common CSCs related factors, SP traits, and sphere formation to identify HNSCC CSCs. However, in solid tumors, CSCs may not express a single marker or even none. In addition, CSCs isolated from cancer cell lines are not representative of solid tumors surrounded by niches. Although we have thoroughly reviewed the potential regulators of HNSCC CSCs, it remains unclear which pathway is dominant for HNSCC CSCs. In addition, CSCs may evolve through genetic instability leading to dynamic expression of markers and regulators. In a recent study, Salazar-García et al. [139] performed whole-exome sequencing to analyze the germinal line, tumor cells, and CSC $ALDH^+$ samples from different HNSCC patients. They found that the difference in genes of oncogenic pathways. Therefore, exploring new ideas and novel strategies is essential to target HNSCC CSCs effectively.

Key molecules involved in the transcription of cancer stem cell genes and premetastatic genes in cancer stem cells

The distinct CSCs population in cancers is different. However, in HNSCC the specific CSCs population are CD133, CD44, CD98, ALDH, CD200, ALDH, CD44, GRP78 and BMI1 [140]. Similarly, CSC various abnormal extrinsic and intrinsic signals including niche, and mutations are involved in pathways deregulation that leading to their maintenance.

The Wnt/β-catenin canonical pathway is initiated when Wnt ligand binds to Frizzled receptor and 5/6 coreceptors protein. This causes the recruitment of Axin and disheveled which prevents the degradation to protection of β-catenin. Free β-catenin complexes with TCF/LEF (T-cell/lymphoid enhancer factors) and regulate the Wnt target stem cell genes. Phosphorylation of CD133 also results to AKT activation and the NF-kB pathway, leading to stemness genes activation. Hypoxia inducible

factor-1-α (HIF1α) and c-Myc (myelocytomatosis) are involved in increase of glycolysis and prevent the oxidative phosphorylation in CSCs. Activation of pyruvate dehydrogenase kinases (PDK1-3) is brought by HIF1α, to stop pyruvate dehydrogenase (PDH), leading to oxidative phosphorylation inhibition. C-Myc has a role in activation of the hexokinase, Glucose transporter -1 receptor, and phosphofructokinase which are in favor of glycolysis [140].

Moreover, the activities of CSCs are governed by numerous pluripotent transcription factors. Some of these factors are Oct4, Sox2, Nanog, Kruppel-like factor 4 (KLF4) and Myc. Besides these pluripotent transcription factors, several intracellular signaling pathways, such as Wnt, NF-κB, Notch, Hedgehog, JAK-STAT, TGF/SMAD, and PPAR along with external factors like vascular niches, hypoxia, tumor-associated macrophages, cancer-associated fibroblasts or mesenchymal stem cells, extracellular matrix, and exosomes play vital roles in the regulation of CSCs [141]. A favorable microenvironment is required for cancer development. Some studies showed intercellular communications are mediated by microvesicles (MVs) released by cells. Large MVs are produced by the tumor cells and released in the circulation and other biological fluids [142, 143]. These MVs have the pleiotropic effect, enabling their involvement in cancer development, progression, and premetastatic niche formation [144]. Normal stem cells are an important source of MVs that may act as paracrine mediators of genetic information through horizontal transfer [145-148]. The transmembrane glycoprotein CD44, a common stem cell niche component, integrates signaling in normal stem cells, cancer stem cells, and (pre)metastatic niches [149]. The biological markers of stem cells in pancreatic CSCs (Pan-CSC) include CD44v6, c-Met, Tspan8, alpha6beta4, C-X-C-chemokine receptor 4 (CXCR4), CD133, epithelial cellular-adhesion factor (EpCAM) and claudin7 [150], breast stem cancer cells such as ALDH1A1 (aldehyde-dehydrogenase 1 family member-A1) [151, 152], and brain CSCs such as CD133 and in HNSCC such as $ALDH^+$, $CD44^+$, $CD166^+$ [153-155] have been investigated. Cancer stem celllike phenotype and the difference in the gene expression pattern responsible for diverse biological roles in HNSCC has been studied recently. Hypoxia-regulated genes have been shown to be helpful for the prediction of radiotherapy responses in HNSCC patients [156]. The biological role of polycomb (PcG) genes *Bmi1* and *TERT* in tumorigenesis in human stromal cells which were immortalized as the HNSCC model studied recently. It was found that *Bmi1* was predominantly expressed in early head and neck squamous cell carcinoma, indicating that the PcG is essential in early cancer development [157]. The role of the p53-p16/RB pathway in HNSCC can be focused on interpreting the early carcinogenesis of HNSCC for better management. Besides, m6A modulators have been emerging cancer progression molecular mechanisms [158].

Stem cells regulators

CSCs have the ability of self-renewal, that may lead them to tumorigenesis [159]. The symmetrical division of CSCs divide them into two CSCs or, in other hand into one CSC and one daughter cell [160]. The symmetrical splitting manner of CSCs expand them to excessively increase cell growth, resulting in formation of tumor [161]. Normal stem cells and CSCs follow same regulatory signaling pathways, for example the Wnt/β-catenin [162], Sonic Hedgehog (Hh) [163], and Notch pathways. These pathways are involved in the self-renewal process [164]. Besides, other signaling molecules, for example PTEN and the polycomb family, are involved in the regulation of CSCs cycle [165].

Several factors are involved in the regulation of stem cells. These might be transcription factors which play a basic role in the proliferation of stem cells. Reprogramming of somatic stem cells can be can be carried out to generate iPSC by increasing the expression of the transcription factors such as Octamer transcription factor4 (Oct4), Sox2, Nanog, KLF4, and Myc [166, 167]. Besides, SRY and Oct4 are considered as potential differentiation therapy targets in stem cells. The over-expression of Sox2 transcription factor in basal-like breast cancer may be supportive to characterize the cell phenotypes of poorly differentiated/stem cells [168]. The deletion p53 and Myc synergizes to induce proliferation and tumorigenesis in hepatocytes [169]. Besides the loss of p53, Bcl-2 and BMI-1 overexpression and deletion of p19ARF also shown the regulation of Myc in CSCs survival and proliferation [170]. In addition, the perturbance of Myc results in

Hepatocellular carcinoma stem cells differentiating into hepatocytes and biliary duct cells resulting the formation of bile duct structures [171].

CSCs have multipotential characteristics. They can also differentiate into other cell types in addition to their self-renewal capabilities. Bonnet and Dick [172] showed that $CD34^{++}$/$CD38^{-}$ LSCs (Leukemia stem cells) were able to differentiate and proliferate in severe combined immunodeficient mice. CSCs isolated from the brain of patients are positive for the markers CD133 and nestin [173]. CSCs from the breast indicated varied expression patterns of surface biomarkers. Some of these surface biomarkers are $CD44^{+}$, $CD24^{-}$, SP, and $ALDH^{+}$ [174-176]. $CD271^{-}$ or $CD271^{+}$ melanoma stem cells were able to generate tumors in SCID mice [177].

Initial steps on targeting CSCs

Post-therapy recurrence and metastasis are related to residual CSCs. Therefore, effectively eliminating the subpopulation CSCs is essential in anti-cancer activities [178]. Therefore, much effort is needed to target HNSCC CSCs in preclinical studies.

Small molecular target drugs

Some authors reported that some molecular target drugs could eliminate HNSCC CSCs in vitro (Table S2). EGFR is one of the four members of the HER tyrosine kinase (RTK) receptor family, composed of EGFR/HER1/erbB1, HER2/erbB2, HER3/erbB3, and HER4/erbB4. The receptors of RTK, such as epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α), can activate intracellular signaling pathways that control growth, differentiation, survival, and invasion [179]. The overexpression of EGFR is a frequent molecular alteration associated with aggressiveness, resistance to treatment, and poor clinical outcomes in HNSCC [180]. Therefore, the EGFR-targeted drug cetuximab has been recommended as a clinical combination with dihydropyrimidine dehydeogenase (DDP)-based chemotherapy as an anti-HNSCC treatment in NCCN guidelines. However, resistance to chemotherapy still exists. Recently, it's been reported that combining Cetuximab and Erlotinib could induce CSCs differentiation and transit EMT-CSCs back to the epithelial phenotype, which sensitizes treatment and restricts local invasion and metastasis [181]. More recently, Roy S et al. [182] found that Afatinib, the second generation of FDA-approved pan-EGFR inhibitor, could inhibit the growth of HNSCC CSCs in vitro and in vivo by inducing severe apoptosis and an uncommon weak protective autophagic response preferentially in stem-like HNSCC cells [183]. However, CSCs usually have low EGFR expression and overexpress the anti-apoptotic Bcl-2 protein [184]. Anti-apoptosis members of the Bcl-2 family are associated with a poor prognosis of HNSCC. ABT-737 is a well-characterized BH3 mimetic that prevents binding ligands to anti-apoptotic Bcl-2 family protein and indirectly activates the pro-apoptotic Bcl-2 family members. Marion Gilormini et al. [185] suggested that ABT-737, alone or in synergism with radiation, can efficiently eliminate stem-like quiescent HNSCC cells in vitro and synergistically inhibit the growth of xenograft tumours. Another group observed the combined effect of ABT-199, Bcl-2 inhibitor, cetuximab, and radiation as anti-CSCs [186]. The combination significantly inhibited proliferation, invasion/migration, and resistance to apoptosis of HNSCC CSCs in vitro and strongly reduced the tumor growth and increased in vivo survival without side effects. Like EGFR, Lin28, an essential RNA-binding protein, also plays a critical role in regulating the balance between stemness and differentiation in embryonic stem cells (ESC) [187]. Chen and coauthors [188] showed that the combination of C1632 (Lin28 inhibitor) and metformin (anti-CSCs hypoglycemic medication) exerts synergistic anti-tumor effects in OSCC cell lines and xenograft tumor growth. Bruton's tyrosine kinase (BTK), a cytoplasmic non-receptor tyrosine kinase, is upstream of the phosphoinositide 3-kinase (PI3K-AKT) pathway, phospholipase-C, protein kinase-C, and NF-κB, performing many functions, including cellular differentiation, proliferation, and adhesion to innate and adaptive immune responses [189]. Although BTK is mostly involved in the hematologic tumor, it is expressed aberrantly in concurrent chemoradiotherapy (CCRT) resistant OSCC tissues, correlated with stemness and EMT factors, and influences survival rate. The Ibrutinib, a first-class BTK inhibitor, reduced CSCs number and increased the DDP sensitivity of OSCC SP-derived cells [190]. Glycogen

synthase kinase 3β (GSK3β) controls the shift from EMT-CSCs to CSCs-epi. Hideo et al. demonstrated that GSK3β inhibition induced mesenchymal-to-epithelial transition (MET) from CD44 (high)/ESA (low) cells to CD44 (high)/ESA (high) cells and pre-existing CD44 (high)/ESA (high) cells to differentiate. The CD44 (high)/ESA (low) cells overexpressed dihydropyrimidine dehydrogenase (DPD), a factor affecting the therapeutic sensitivity to 5-FU. Combination of both DPD inhibitor, 5-chloro-2,4-dihydroxypyridine (CDHP) and GSK3β inhibitors markedly enhanced 5-FU-induced apoptosis of CD44 (high)/ESA (low) cells [191]. In addition, the Wnt/β-catenin signal is another CSCs regulating pathway. Tankyrases are members of the poly (ADP-ribose) polymerase (PARP) family proteins, which serve as regulators of the canonical Wnt/β-catenin signaling [192]. XAV-939, a small molecule of tankyrase inhibitor, reduced CSCs-mediated chemoresistance in DDP-resistant HNSCC cell lines combined with DDP via DNA damage [193]. Similarly, a recent study identified LF3, a 4-thioureido-benzenesulfonamide derivative, as a potent and specific inhibitor of activated Wnt/β-catenin signals [194]. In this study, the self-renewal capacity of head neck CSCs was blocked by LF3, as examined by sphere formation. Beside, secreted frizzled-related protein 4 (sFRP4) is one of five members of the sFRP family and a naturally extracellular inhibitor of Wnt signaling [195]. Warrier's group showed that sFRP4 decreased the expression of CSCs markers (CD44 and ALDH) and inhibited proliferation, EMT, and enhanced chemosensitivity of HNSCC CSCs [196]. Moreover, histone deacetylases (HDACs) regulate several genes involved in cancer initiation and aggressiveness [197]. Similarly, Royal jelly acid showed suppression in HCC tumorigenicity that inhibited H3 histone lactylation targeted H3K9la and H3K14la sites [198]. In addition, transcriptome analysis of transgenic mice models predicted several oncogenes in brain [199], lungs [200].

Studies demonstrated that HDACs inhibitors (HDACi), suberoylanilide hydroxamic acid (SAHA), and trichostatin A (TSA), inhibited the stemness of HNSCC CSCs, and enhanced the DDP sensitivity, which may be attributed to reduced NANOG and Survivin expression [201, 202]. Similarly, valproic acid (VPA), another HDACi, inhibited the self-renewal abilities of HNSCC CSCs with decreased expression of CSCs markers, such as Oct4, Sox2, and CD44, and enhanced sensitivity to DDP via reducing ABCC2, six and inducing apoptosis. The VPA combined with DDP attenuated xenograft tumor growth [203]. Entinostat, another HDACi, could induce cycle arrest (G0/G1 phase), tumor apoptosis and increase in ROS production, and significant reductions in HNSCC CSCs [204]. In addition, cancer cells have a super capacity to ROS *scavenger* via redox enzyme. Therefore, combining dimethyl fumarate (DMF), a GSH (glutathione) inhibitor, and Buthionine sulfoximine (BSO), a GSH synthesis inhibitor, could sensitize HNSCC CSCs to radiotherapy. It suggests that reduced antioxidant capacity may be a striking strategy to target CSCs [205].

Another reason for the radio-resistance of HNSCC CSCs is an extended G2/M arrest phase. Therefore, UCN-01, a checkpoint kinase (Chk1) inhibitor, and all-trans retinoic acid (ATRA), an inducer of differentiation, combined with irradiation drastically decreased the surviving fraction of HNSCC CSCs [206]. MEDI-5117 is an IL-6 inhibitor. Finkel and coauthors found that low-dose MEDI5117 antibodies decreased the CSCs fraction in three low-passage patient-derived xenografts (PDX) models of HNSCC [207]. They conducted a clinical trial in which MEDI5117 prevented tumor recurrence when used in the adjuvant setting. BMI-1, downstream of IL-6, is a CSCs-related factor. Jia et al. [208] demonstrated BMI-1$^+$ CSCs contributed to the failure of PD-1 and DDP treatment in an HNSCC mouse model. PTC209 plus PD-1 inhibitor could eliminate CSCs via recruiting CD8$^+$ T cells and prevent the progression and relapse of HNSCC. Meanwhile, an inhibitor of the IL-6R/BMI-1 axis, Tocilizumab, could target HNSCC CSCs via reversing DDP-induced self-renewal and chemoresistance in DDP-resistant HNSCC cells [209]. COX-2 is an inducible enzyme that triggers the biosynthesis of prostaglandins. Celecoxib, a COX-2 inhibitor, inhibited RNA expression of stemness-related genes and sphere formation in HNSCC cell lines [210].

Compounds extracted from natural herbs

Although targeted molecular drugs have shown the ability of anti-HNSCC CSCs experimentally, resistance is a challenging problem clinically.

These causes include activating mutations in the target itself and activating various compensatory pathways and EMT as a major mechanism of resistance [211]. Emerging evidence demonstrates that pure compounds extracted from natural herbs or plants exhibit features of multi-targets, anti-CSCs, and less toxicity. *Ovatodiolide (OV)*, a bioactive chemical substance purified from *Anisomeles indica* (L.) Kuntze (Labiatae) could inhibit NPC tumor sphere formation, attenuate NPC stem cell tumorigenicity, and enhance the sensitivity via reducing the expression of p-FAK, p-PXN, F-actin, slug proteins, SOX2, OCT4, and JAK-STAT signaling pathway [212]. In addition, *Epigallocatechin-3-gallate (EGCG)* is active polyphenolic catechin purified from *green tea*. Lee et al. examined the anti-tumor effect of EGCG on HNSCC CSCs. They demonstrated that EGCG inhibits the self-renewal capacity of HNSC CSCs via inhibition of stem cell markers, such as Oct4, Sox2, Nanog, CD44, ATP-binding cassette subfamily-G member-2 (ABCG2), and Notch signaling [213].

Quercetin is a polyphenolic flavonoid compound in nuts, teas, vegetables, herbs, and people's daily diets [214]. Chang et al. found that Quercetin could reduce the stemness of HNSCC CSCs through the decreased expression of Twist, N-cadherin, and Vimentin [215]. Besides, Deng's laboratory identified a new gamboge derivative compound 2 (C2). In their study, C2 treatment reduced colony formation of HNSCC CSCs and inhibited expression of CSCs markers (CD49f, CD133, and CD44) more significantly than DDP with less toxicity. The inhibition effect of C2 on CSCs was attributed to targeting Ki-67, phosphor-EGFR, CD49f, and CD133 [216]. *Cucurbitacin I* is a natural triterpenoid isolated from the *Cucurbitaceae* family plants and other plant types. Chen et al. found that *Cucurbitacin* I could inhibit the proliferation, tumor aggressiveness, and stemness signatures and induce apoptosis, differentiation, and radiosensitivity of HNSCC CSCs via suppression of STAT3, Janus-activated kinase 2 (JAK2), Bcl-2, Bcl-xL, and survivin [217].

Chang et al. screened for active components and discovered YMGKI-1 and YMGKI-2 from Antrodia cinnamomea Mycelia (ACM) natural products. They demonstrated that both components inhibited stemness, decreased expression of CSC markers, and promoted radiosensitivity of HNSCC CSCs by downregulating the activated autophagic signaling pathways, STAT3 and Src [218, 219].

In addition, *Plumbagin* (5-hydroxy-2-methyl-1,4-naphthoquinone, PLB) is a small molecular compound derived from the root of *Plumbago zeylanica L*, *Juglans regia, Juglans cinerea,* and *Juglans nigra*, with a variety of pharmacological activities. Recently Pan et al. [220] reported that PLB-induced apoptosis inhibited EMT and stemness and promoted MET via mediating multiple targets on tongue squamous cell carcinoma (TSCC) cell line SCC25 cells. In addition, translation inhibition could disrupt stemness properties [220]. *SVC112* is a synthetic derivative of the cyclic hexapeptide bouvardin, a plant-derived translation elongation inhibitor with less toxicity. Keysar et al. demonstrated that SVC112 inhibits tumorsphere growth and enhances radiosensitivity in vitro by suppressing Myc, Cyclin D1, Myc, and Sox2. SVC112 alone and with radiation inhibits the growth of tumours and CSC in vivo [221]. Besides this, *Lovastatin (LV)* is a natural lipophilic statin derived from *Monascus* or *Aspergillus*-fermented rice and Dioscorea. In Peng et al.'s study, LV inhibited proliferation and self-renewal and induced apoptosis and cell cycle arrest of NPC CSCs. LV could also synergistically enhance the sensitivity of NPC CSCs to chemotherapy and photodynamic therapy [222]. *Tetrandrine* is a bis-benzylisoquinoline alkaloid isolated from *Stephania tetrandra* and other related species of *Menispermaceae.* Cui et al. demonstrated that tetrandrine inhibited the cell viability and proliferation of CD133 in Hep-2 cells by impacting the cell cycle and enhancing cell apoptosis via upregulating Bax and caspase-3 and downregulating Bcl-2 [223]. *Isoliquiritigenin* (ISL) is a natural flavonoid compound derived from the natural herb *licorice root (licorice)* with significant anti-tumor ability. Hu et al. showed that ISL was more cytotoxic to OSCC CSCs and hindered self-renewal by reducing ALDH1 enzymatic activity and CD44 positivity in OSCC-CSCs. ISL also enhanced sensitivity to DDP via inhibiting ABCG2. Finally, they demonstrated that the anti-CSCs ability of ISL was ascribed to regulating the protein expression of mRNA and membrane GRP78 [224]. *Sulforaphane (SF)* is an isothiocyanate isolated from *broccoli*.

Elkashty et al. found that SF-combined treatments inhibited the colony formation of HNSCC CSC and in vivo tumor progression with potential mechanisms including the stimulation of caspase-dependent apoptotic pathway, inhibition of SHH pathway, and decreased expression of SOX2 and OCT4 [225]. *Curcumin* is a bioactive polyphenolic compound identified in turmeric with significant anti-tumor ability. However, the low solubility in aqueous media, poor bioavailability, and pharmacokinetic profiles limit its therapeutic potential. Therefore, several different formulations have been produced. Recently Basak et al. found that Curcumin-difluorinated (CDF), a synthetic analog of curcumin, was packaged in liposomes and used to evaluate the growth inhibition of DDP-resistant HNSCC cell lines. Treatment with liposomal CDF resulted in a statistically significant tumor growth inhibition in nude mice xenograft and a reduction in the expression of CD44, indicating an inhibitory effect of liposomal CDF on CSCs [226]. In addition, curcumin and metformin combination could prevent 4-nitro quinoline-1-oxide (4NQO) induced oral carcinogenesis in a mice model through an overall downregulation of CSC markers [227]. *Isoorientin* (3',4',5,7-tetrahydroxy-6-C-glucopyranosyl flavone) is a C-glycosyl flavone extracted from *Aspalathus linearis* and several other plant species. In Liu et al.'s study, Isoorientin could significantly reduce the expression of p-STAT3, Wnt/β-catenin, p-GSK3, and downstream effectors transcription factor-T cell factor 1 (TCF1) and LEF1, enhance DDP toxicity, and inhibit the tumorigenicity and growth of OSCC all in all attributing owing to targeting OSCC-SC-mediated stemness [228]. *Apigenin* (4',5,7-trihydroxyflavone) is one of the most studied phenolics abundant in fruits and vegetables. The compound could significantly down-regulated expressions of CSCs markers, CD44, NANOG, and CD105 of HNSCC cells and reduce the number of cells expressing CSCs markers under hypoxia [229]. Resveratrol (trans-3,5,4'-trihydroxystilbene) is a phytoalexin initially found in *Polygonum cuspidatum*. In Hu et al.'s study, resveratrol reduced the activity of CSCs markers (ALDH1 and CD44) and CSCs-related gene expressions (Oct4, Nanog, and Nestin) in HNC-CSC and regulated EMT-related markers in vitro and in vivo, which may lead to a valuable clinical therapeutics combining with conventional chemotherapy modalities for HNC [230].

Silibinin is a flavonolignan extracted from the fruit and seeds of *Milk thistle*. It is well-known for its hepatoprotective and anti-carcinogenic effect on various experimental cancer models. Chang et al. showed that Silibinin exerted an inhibitory influence on invasion, stemness, EMT, and anti-apoptosis ability of HNC-CSCs via activation of miR-494-inhibiting Bmi1/ADAM10 expression [231]. Recently in an in vitro study, *Propolis* could reduce CSCs numbers and decrease CSCs markers specifically [232]. The effects of the compounds mentioned above are summarized in Table S3.

Immunotherapy

In addition to specific formulation, Immunotherapy targeting CSCs provides another promising perspective. Liao T et al. [233] tested responses against putative HNSCC CSCs by an alloantigen-specific model system in vitro. Although CSC populations were less sensitive to major histocompatibility complex (MHC) class I-restricted alloantigen-specific $CD8^+$ CTL lysis, IFN-γ pretreatment upregulates molecules essential for antigen processing and presentation, leading to over-proportionally enhanced lysis of CSC-enriched spheroid culture-derived cells (SDC). Moreover, the subset of $ALDH^{high}$ CSCs presented more sensitivity toward $CD8^+$ CTL killing than the $ALDH^{low}$ SDC. The in vitro experiment by Liao T et al. suggested that Immunotherapy targeting $ALDH^+$ CSCs may be a promising approach. In a preclinical study, researchers induced and expanded human leukocyte antigens (HLAA2) restricted, ALDH1A1 peptide-specific $CD8^+$ T cells by *in vitro* stimulation of $CD8^+$ T cells isolated from peripheral blood from regular HLA-$A2^+$ donors. These HLA-A2-restricted, ALDH1A1 peptide-specific $CD8^+$ T cells recognized and eliminated $ALDH^{bright}$ cells, specifically in vitro and in vivo. They showed that the adoptive transfer of ALDH1A1-specific $CD8^+$ T cells inhibited the growth of primary and metastatic tumors in xenografts [234].

Novel radiotherapy

Surgery and radiation are the mainstream in HNSCC therapy. HNSCC CSCs resistant traditional photon radiation and EGFR inhibitors; moreover, IR can activate EMT and the CSC phenotype [235]. However, in recent in vitro research, carbon ion irradiation effectively

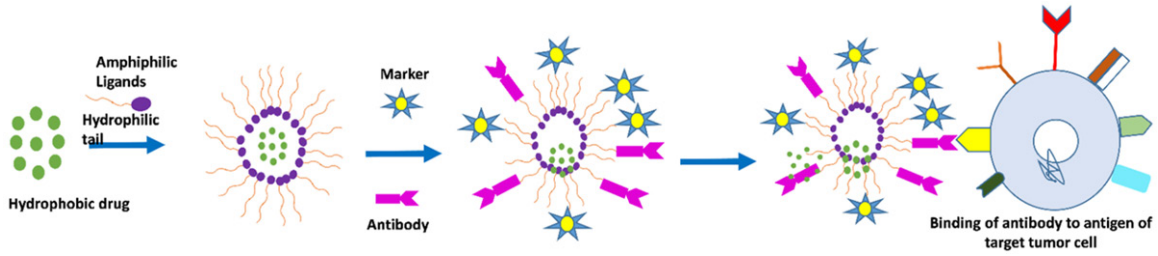

Figure 2. Overview of targeted drug delivery. The drug molecules (green) are surrounded by amphiphilic ligands with a hydrophilic tail. Attached to the tail of this amphiphilic ligand are markers and antibodies. These antibodies bind with surface-specific receptors on tumor cells in the drug and are released there to initiate apoptosis in HNC.

reduced migration/invasion of HNSCC CSCs and non-CSCs alone or combined with cetuximab [236]. More recently, a study showed that daily photobiomodulation with 3 J/cm^2 suppressed cellular viability and that 6 J/cm^2 decreased the number of spheres of OSCC cell lines and the expression of the CSC-related gene BMI1 [237]. Yu et al. demonstrated that topical 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) inhibited the ALDH1 activity of HNSCC cells, eliminated self-renewal capacity, CD44 positivity, stemness signatures, and enhanced chemosensitivity in HNSCC CSCs [238, 239].

Potential strategies

Given the therapeutic options above-mentioned, personalized treatment may be a good one to solve the problems. We can identify primary CSCs markers and regulators and then take adequate measures to target CSCs in individual HNSCCs. Based on individualized treatment: 1) Local CSC-targeted DDSs. It may be a promising approach to apply peritumoral injections using pure natural compounds with multi-targets and less toxicity as anti-CSCs formulations, such as nanoparticles, and in combination with radiation. Local CSC-targeted DDSs are better than conventional IVs. It could withstand the barrier of the niche, ensure anti-CSC agents arrive at the targeted CSCs, and can be taken up by CSCs with enhanced permeability and retention effect (EPR). 2) Immunotherapy targeting CSCs in individual HNSCC treatment. 3) The biology of CSCs depends on the niche; double targeting cancer stemness and the niche, such as hypoxia, microcirculation, or immune status, is a possible approach. Chinese traditional medicine (TCM) has its principle of the human environment, for instance, the Yin-Yang theory. According to the theory, illness is due to the imbalance of two opposing forces of energy, Yin and Yang. In addition, the compounds mentioned above extracted from Chinese traditional herbs (TCH) exhibit anti-CSC effects. Pure combined compounds with fewer toxicities like Cocktail therapy, may have a promising prospect, and TCH carried by novel DDSs may be another promising strategy. In general, the anti-CSCs strategy seems a promising therapeutic option, although there is still a long way to go for successful clinical application.

Targeted drug delivery in HNSCC

Although the drug monomer presents an anti-CSCs effect, targeting CSCs requires unique drug delivery systems (DDSs) formulation, as shown in **Figure 2**. Su et al. [240] synthesized and characterized anti-CD44 antibody-coated superparamagnetic iron oxide nanoparticles (SPIONPs). The exploration of the formulation was dependent on the mechanism of hyperthermia therapy. The CD44-SPIONPs (superparamagnetic iron oxide nanoparticles) target CD44$^+$ HNSCC CSCs by endocytosis, which could generate heat through magnetic vector and physical rotation under an alternating magnetic field to kill CSCs. After the AMF treatment, CD44-SPIONPs induced CSCs to undergo programmed death with an inhibitory ratio of 33.43%, significantly inhibiting the growth of grafted Cal-27 tumors in mice. In addition, Miyano et al. [241] used cyclic Arg-Gly-Asp (cRGD) peptide, an HNSCC CSCs marker specific binding to integrin $\alpha_v\beta_3$, on micellar nanomedicines incorporating cisplatin (cRGD-installed DDP/m). The cRGD-installed DDP/m showed significant antitumor activity against primary HNSCC xenograft tumors, with the rapid accumulation of the metastatic lymph nodes leading to prolonged mice survival.

RNAi therapies remain unsatisfactory due to delivery limitations by many factors, such as easy degradation by enzymes. Lo et al. [242] provided a feasible non-viral gene delivery method, cationic polyurethane-short branch polyethyleneimine (PU-PEI)-based delivery of nuclear localization signal (NLS) pre-conjugated dsDNA encoding siRNAs. In their study, co-administrated PU-PEI vehicles containing NLS-pre-conjugated dsDNA encoding either siEZH2 or siOct4 remarkably achieved gene silencing, which led to diminished CSC-like properties, suppression of EMT, enhanced radiosensitivity, and prevention of metastasis in HNSCC. Meanwhile, nano micelles could load multiple agents to target different subpopulations. Recently, Zhu et al. developed salinomycin (SAL)-loaded poly (ethylene glycol), 2000-di-stearoyl phosphatidyl-ethanolamine (DSPE-PEG)-methotrexate (MTX) nano micelles (M-SAL-MTX), for SAL targeted $CD133^+$ CSCs and MTX could kill non-CSCs. In their study, M-SAL-MTX effectively accumulated in tumor tissues compared with a single treatment of SAL or MTX; therefore, M-SAL-MTX exhibits significant anti-CSCs and anti-non-CSCs in vivo [243].

In addition, peritumoral injections are available in HNSCC. Hyaluronic acid (HA) is a particular ligand for the CD44 surface receptors. Peritumoral injections of cisplatin conjugated to nanoscopic (25-100 nM) particles of HA (HA-cisplatin) provide superior antitumor efficacy and CSCs targeting compared to conventional IV cisplatin therapy in a laryngeal cancer xenograft model with less toxicity [244]. It may be useful in nanoparticles targeting CSCs markers with a specific route of administration may be a promising strategy to target CSCs.

Recent advances in cancer genetics, sequencing, and their role in therapeutic efforts have led to precision medicine. Precision medicine is mainly based on the genetic, environmental, and lifestyle characteristics that can lead to identifying the therapy for individual patients. Although this approach is very effective in oncology, some issues are still there, including drug resistance and toxicities. Drug delivery systems have enabled the modulation of pharmacological parameters, including stability, pharmacokinetics, absorption, and exposure to tumors and healthy tissues.

Nanomedicine is very helpful in targeted drug delivery, decreasing the drug toxicity to non-target cells compared to non-carrier drugs [245]. Currently, different types of nanoparticles (NPs) have been reported and approved by US Food and Drug Administration [246] for cancer diagnosis and treatment. These are organic NPs (polymer, dendrimer, ferritin, and micelles) and inorganic (Q dots, silver iron oxide, gold). The NPs technologies have greatly improved controlled drug releases and enhanced the targeting of drug delivery to specific tissues [247-249]. These advantages of NPs drug delivery systems are improving the current treatments and paving the way for new therapy options. To cover the significant issues of medicines, including solubility and bioavailability, long time circulation, and unwanted toxicity to neighboring healthy tissues, phytomedicine integration into nano vehicle is a valuable and productive choice to enhance its biological effects and overcome the physiological barriers [250, 251].

Nanotechnology-based targeted drug delivery system for HNC therapy is alternatives treatments that maximize the efficacy and offer good efficacy to the problems compared to conventional therapies. A targeted drug delivery system reduces the rate of delivery failures and cell death and minimizes multidrug resistance. These properties of NPs are promising in HNC treatment because to reach the target, the therapeutic targets need to cross biological barriers, including the blood-brain barrier, which is a significant obstacle and reduces drug delivery to the brain [252]. To overcome the shortcomings of conventional methods in HNC management, using nanocarriers as diagnostic and therapeutic agents has improved efficacy and safety. The NPs guide anti-cancerous drugs to the target cells, increasing the concentrations of drugs in the intracellular environment of the target cells and reducing the toxicity to normal cells. They attach specific receptors to the target cells on the surfaces and are internalized by endocytosis.

Targeting through nanocarriers

Nanocarriers are the most effective system to deliver the anti-cancerous agent at the site of interest using passive or active targeting approaches. The system enhances the drug concentration in HCN target cells, increases retention, and reduces toxicity to normal cells [253, 254]. They are targeting through nanocarriers

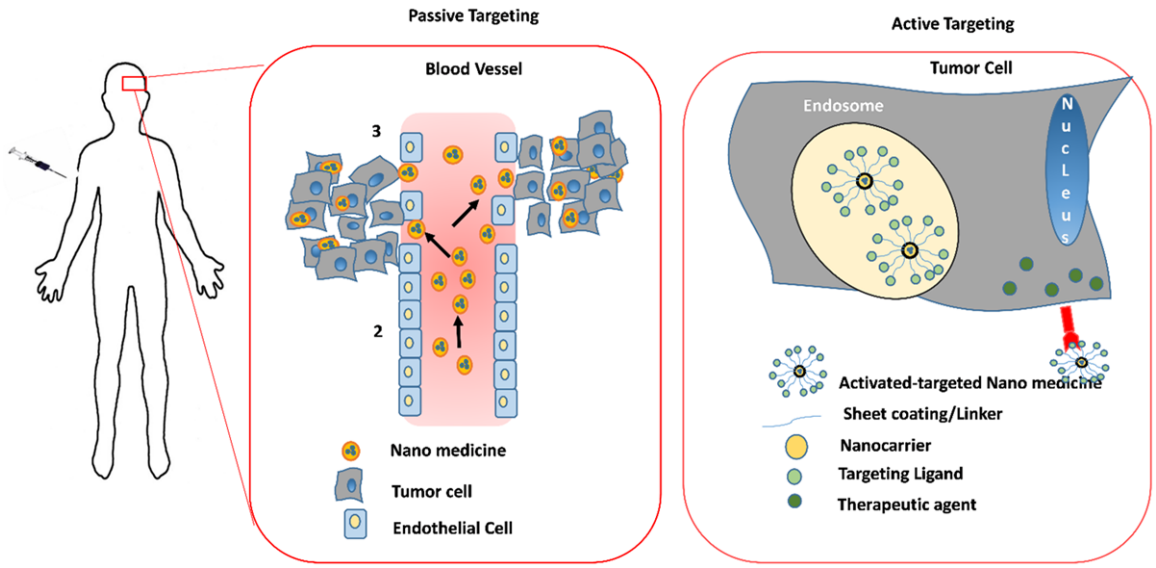

Figure 3. Flowchart mechanism of active and passive targeting.

involving active and passive approaches. Active targeting consists of using ligands/drugs to the site of interest in HNC, while passive targeting is without any stimulus or ligand to the target site.

Passive targeting

Passive targeting involves the systemic administration of nanocarriers, which tend to accumulate selectively at the desired location as a result of the enhanced permeability and retention (EPR) phenomenon [255]. The EPR may be influenced by different tumor microenvironment factors (TME), including vasculature, stage, macrophages, interstitial, and lymphatics fluid pressure [256, 257]. Thus, the anatomy and physiological conditions of the target are essential for passive targeting. The blood vessels are produced in high quantities in tumoral tissues promoting rapid growth that allows nanocarriers to be easily retained in tumor tissues of HNC [257].

Active targeting

Active targeting involves the specificity and designing of the nanocarrier to attach to the target site [255]. All NPs exhibit a good conjugation capability with target ligands, including antibodies, sugars, nucleic acids, peptides, vitamins, and other small molecules. The nanocarrier is conjugated with a molecule with a good binding affinity to attach firmly to the target tissue [258]. Nanoparticles are attached to targeting ligands and given a reasonable degree of tumor specificity. During the tumor diagnosis/treatment, these drugs/ligands specifically bind to the NP's target and interact with the target cells receptors (which are tumor markers), and endocytosis carries the ligand inside the target cells [259]. In active targeting of HNC, the target cells must have high expressed markers compared to healthy tissues. A flowchart of active and passive targeting is provided in **Figure 3**.

Challenges in active targeting

The critical challenge is selecting a targeting agent to minimize the toxicity to surrounding healthy tissues. Physical/triggered targeting is also a type of active targeting that depends on the usage of internal (pH, enzymes, redox potential) or external (temperature, UV light, ultrasound) stimuli to potentiate the nanocarrier to the site of interest for releasing the drugs molecules [260, 261]. In one of its kind, the magnetic nanocarriers are driven to the target site using external stimuli of the magnetic field.

Nanocarriers for drug delivery

In this segment, our attention is directed towards the most auspicious nanocarriers intended for drug delivery in the treatment of

head and neck cancer (HNC). These include lipid-based, polymer-based, and metallic-based nanocarriers.

Lipid-based nanocarriers

In cancer-targeted drug delivery systems, lipid-based nanocarriers are commonly phospholipids possessing unique properties and self-organization in an aqueous environment to form organized shapes and structures. Lipids may form liposomes, micelles, or bilayers. Micelles and liposomes are the two most commonly used for drug delivery.

Micelles have a hydrophobic core and hydrocarbonated tails surrounded by polar heads. Micelles are formed by amphipathic molecules containing a polar group and a tail with only one hydrocarbon [262, 263]. Concerning HNSCC tumor studies, it has been reported that microRNA-107 is downregulated compared to healthy cells. To deliver the pre-miR-107 successfully, a cationic lipid nanoparticle was developed, consisting of DDAB (dimethyl octadecyl ammonium bromide), cholesterol, and α-Tocopheryl polyethylene glycol 1000 succinate [264].

Liposomes have been used extensively as nanocarriers in cancer therapy. Each liposome consists of a phospholipid bilayer and an aqueous inner cavity, which can encapsulate different types of polar molecules [265, 266]. The nano-formulations are in clinical trials; some have been marketed to treat HNC. Liposomes are an ideal system of nanoencapsulation to carry drugs, overcome pharmacokinetics problems, stability in vivo, and toxicity to healthy tissues. One important example is the encapsulation of curcumin in liposomes.

Curcumin is a component of *Curcuma longa,* possessing the potential property of antibiotic, anti-inflammatory, and antioxidant agent, and it also demonstrated good anticancer activity [267].

Polymer-based nanocarriers

These nanocarriers can be produced from synthetic or natural polymers [268, 269], which are biocompatible, stable, possess toxicity, have no side effects, and are entirely metabolized in the human body. In a previous study, multifunctional polymer-based nanoparticles (Linear dendritic mPEG-BMA4) for targeted delivery of saracatinib (kinase inhibitor) into HNC cells in vivo. Compared with free drugs, the polymeric nanoparticles loaded with saracatinib demonstrated good anticancer activity [270]. Chen et al. reported an injectable, biodegradable polymer, cisplatin, for the human HNSCC treatment. This polymer exhibited a well released (80%) of cisplatin and was significantly involved in tumor suppression compared to free cisplatin [271].

Folate-targeted treatment with methotrexate (MTX) is commonly considered in HNSCC; however, its severe side effects are very severe [272]. Dendrimer-targeted delivery can minimize toxicity and enhance drug efficacy. Ward et al. used cell lines with null, intermediate, and high expression folate receptors and evaluated in vivo efficacy of G5 poly-amidoamine dendrimer-based targeted treatment. The targeted system was more effective against cell lines with high folate receptor expression with increased effectiveness compared to free MTX and control [273].

Metallic nano-carrier

Metallic-based nanocarriers were also found effective in HNC therapy. Zhang et al. used superparamagnetic nanoparticles as a novel targeted drug delivery system for HNCs therapy. A biocompatible mesoporous Fe_3O_4 NPs attached with superparamagnetic polyacrylic acid was developed. These mesoporous Fe_3O_4 NPs delivered bleomycin to the tumor tissue, starting its slow release and the tumor cells apoptosis. The drug also showed significantly reduced side effects of bleomycin to healthy cells. This new approach provided potential applications of mesoporous Fe_3O_4 NPs in HNC treatment using simple technologies, fewer side effects, and more efficacy [274].

Applications of quantum dots (QDs) in HNC

The current applications of magnetic resonance imaging (MRI), X-ray, ultrasound, and radionuclide imaging, to detect and diagnose tumors have limitations. These techniques are less sensitive in detecting malignant cells when small in number, unable to detect biomarkers specific to cancer cells' surface and exhibit hazardous effects to different levels. Thus, in

investigating advanced and novel approaches with fewer dangerous effects and high sensitivity, specificity is of prime importance and urgently required.

QDs, also known as "artificial atoms", is today's most attractive topic in nanobiology. Several researchers are interested in using QDs in cancer diagnostics [275, 276] because; they have excellent resistance to photo-bleaching; secondly, they have good optical properties with superior fluorescence intensity; thirdly, QDs possess multiple fluorescent colors emission under single-source excitation and size-tunable light emission. Furthermore, during the synthesis process, the wavelengths emitted could be tuned and controlled precisely by size and shape. This property is beneficial in performing nanometer resolution and co-localization of multicolor QDs using confocal microscopy. This is also important in reducing the slices of tissue that must be cut for biomarker observation [275-277].

Application of dendrimer nanoparticles in HNC

Dendrimers are synthetic polymers playing an important role in drug discovery and carrier systems [278]. They are "smart" nanocarriers in medicine with multifunctional that can be used in targeted drug delivery of one or more agents selectively to tumor cells with more safety and also to intracellular gene-specific targeting [279, 280]. Dendrimers with nano polymeric designs have been considered a highly specific class delivery system for drugs and genes [281, 282]. Over the past decade, gene therapy has been used in clinical trials. Although there are some drug and gene delivery concepts, including liposomes, viral vectors, cationic polymers, gold, and magnetic nanoparticles [283], however, dendrimers are the most attractive nowadays for their good safety and specificity to the target site [284]. Dendrimers which are 1-100 nm in size, are globular macromolecules consisting of a central core domain, a hyperbranched mantle domain, and a domain of corona with exterior reactive functional groups [285]. These are perfect (spherical) molecules as nanocarriers with specific properties for cell-specific targeting. Dendrimers may be of different kinds, including melamine, poly(propylene imine) (PPI), poly-amidoamine (PAMAM), poly(ethylene glycol), poly(glycerol-co-succinic acid), poly-l-lysine (PLL), triazine, poly(glycerol), poly[2,2-bis(hydroxymethyl) propionic acid], (PEG), and citric acid-based ones [286, 287]. PAMAM and PPI vectors have been extensively examined for medical use [288, 289]. Both have amine-terminated end and pH-dependent drug release properties, making them most suitable for HNC treatment. The dendrimer's 'back folding' or collapse on itself is the most attractive property of dendrimers due to the tertiary amine groups deprotonated at elevated pH [288]. The dendrimer scan traverse several barriers using active and passive tumor targeting.

Recently a poly-amidoamine generation 4 (G4) dendrimer and fluorescently labeled for gene delivery and folic acid-decorated conjugates in HNSCC-targeted have been reported [290]. The G4 dendrimer delivery system is conjugated with folic acid (FA) and has the properties of targeting the moiety of HNSCC. In HNSCC cells, complexing this G4 dendrimer with siRNA or plasmid significantly increases the knockdown system's gene transfection or efficiency. In HNSCC, the G4-FA vector exhibited excellent tumor targeting capability, biocompatibility, sustained retention, and high uptake in a gene therapy approach.

Dendrimers have been synthetically engineered with nanodevices in nanocarrier drug delivery systems. The terminal moieties are responsible for dendrimers' biological effect and global efficiency. Dendrimers in classical drugs overcome the physicochemical limitations, including solubility, stability, specificity, biodistribution, and therapeutic efficiency, **Figure 4**. They have the property to reach the right targets by immune clearance, penetration into cells, and interactions in off-target [291]. All the dendrimers have the desired properties of drug retention, release of the therapeutic agent, unaffecting by the immune system, blood circulation time enhancing, and cells or organs specific targeting [292]. An overview is provided in **Figure 5**.

Different intervention plans in HNC patients

Significant physical and psychological morbidity have been experienced by the HNC patients during radiotherapy (XRT) that not only resulted in the interruption of the treatment, but also quality of life. Intensive radiotherapy (XRT) is carried out in these patients either alone or in

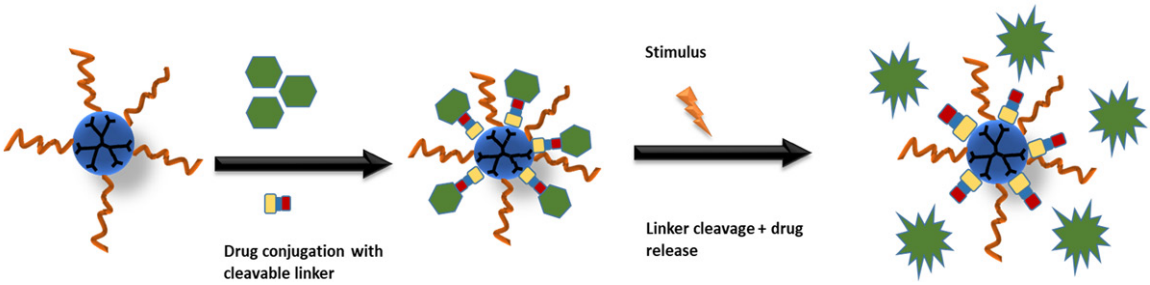

Figure 4. Synthesis of dendrimers and drug conjugation.

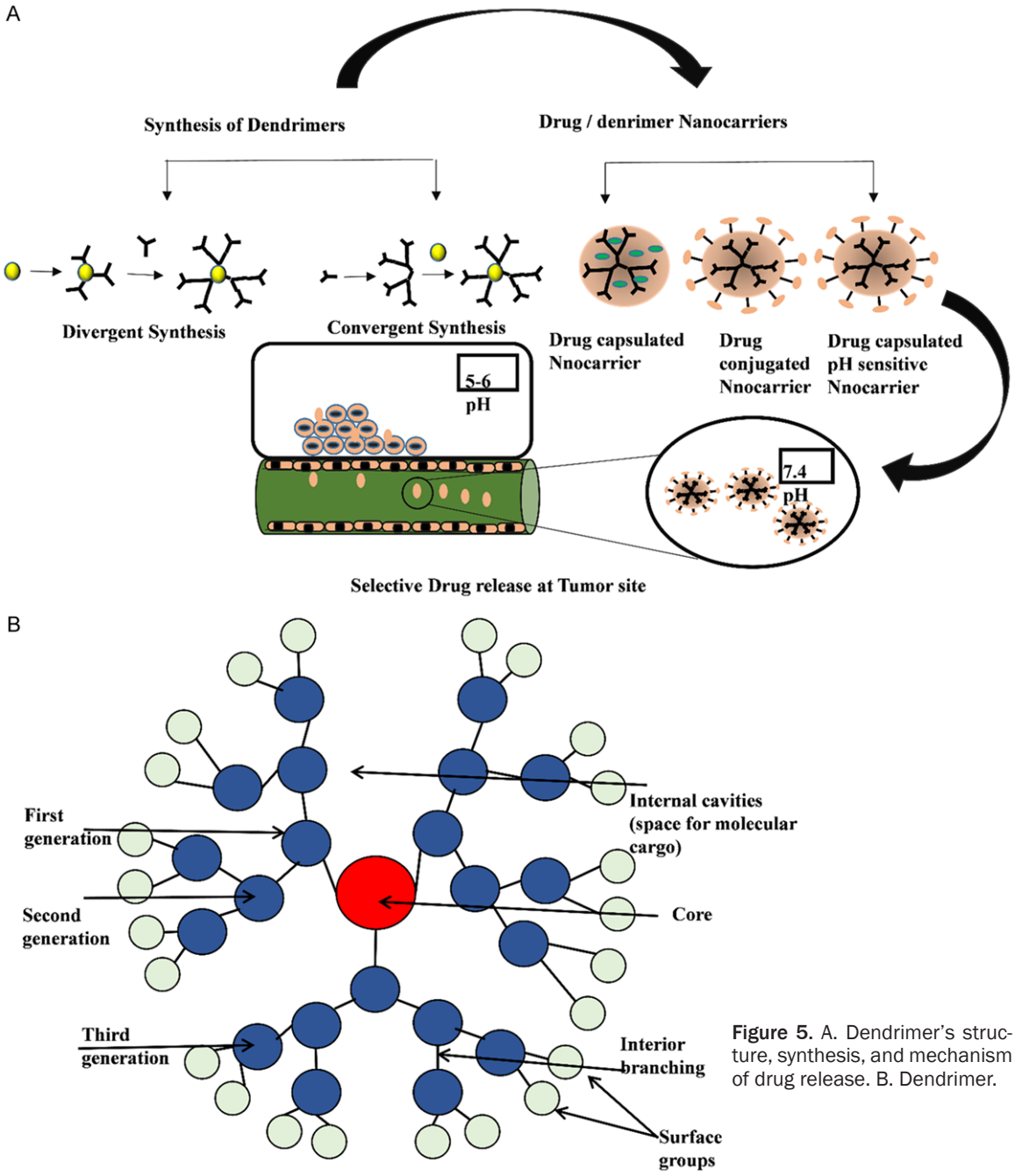

Figure 5. A. Dendrimer's structure, synthesis, and mechanism of drug release. B. Dendrimer.

combination of other treatments [293]. Different interventions have been applied for cancers prevention and control. However, for HNC survivors the interventions so for, may not address the general health and cancer related needs. A study developed a couple-based intervention called "Spouses coping with the Head and neck Radiation Experience" abbreviated as SHARE, was delivered through phone. This intervention supports psychoeducation that encourages self-management and teaches strategies to improve teamwork and coping. The study evaluated couples on self-management and coordination of care and support at the start of XRT to control/alleviate symptom burden (physical and psychological) and improve both partner's adjustment. The results of the study supported the feasibility, acceptability, and preliminary efficacy of SHARE [294]. The successful treatment of HNCs can be based on the TNM (tumor, node, metastasis) staging system. A study based on Polish patients found concordance between clinical and pathological T and N stages in patients with HNCs. It was found that there is a moderate agreement between the clinical and pathological stages for stage T, while substantial agreement was found for stage N [295].

Focused on improving quality of life (QOL) and/or mood in HNC patients, a team of researchers reviewed the available literature and targeted the types of interventions such as educational, psychosocial, physical, and psychological symptom management, mindfulness, pharmacologic, exercise, and telemedicine. Preliminary feasibility and acceptability with some positive impacts on QOL and/or mood were found in HNC patients [296]. PRO-ACTIVE trial intervention in HNC patients suggested useful modifications in telehealth [297].

A more recent study investigation the impact of cognitive behavioral intervention on HNC and treatment on eating and talking, and health-related quality of life of survivorship [298]. This study reports that impact treatment can be particularly distressing and markedly changed activities among survivors. Engaging in therapeutic approaches to manage distress in treatment time may influence quality of life and mood of survivorship phase.

Another study applied Navigation for Disparities and Untimely Radiation Therapy, a multi-level intervention to evaluate feasibility, preliminary efficacy, and acceptability in HNC. They found that the potential postoperative radiation therapy has been improved [299].

A previous study also applied the telehealth intervention in HNC treatment. It was observed that the telehealth intervention is also feasible and acceptable for better management of treatment for HNC [300].

Exercise has also been regarded as a potential intervention in prevention of different types of cancer. During the investigation regular exercise was also found to be a promising intervention in HNC patients. The patients were active participants in a six-week supervised exercise intervention in HNC treatment [301].

Conclusion

HNC has been ranked sixth among the most common cancer worldwide, and its occurrence is still increasing in the future. Due to the failure of HNC treatment, there is an urgent need to design innovative techniques for better management of HNC. Using the advanced approaches of NPs, drug concentration may be increased at the target site. There are several studies available who have evaluated HNSCC patients' tumors or tissues, but the outcomes of the clinical data are not satisfactory. To establish clinically significant CSC markers in the head and neck regions, the primary barrier is that this region is secondary to the convention of amassing malignancies from different upper aerodigestive regions with diverse embryological and biological features. As a result, there is little definitive data about clinical implications of CSCs within HNSCC, the primary exception being prognostic value. Another reason might be due to no single biomarker for CSCs in HNSCC is available. In this context, nanomedicine emerged as an alternative and potential approach to using nanocarriers, which the body's immune system could not sense. NPs have the potential to improve treatment efficiency without harming normal cells. Moreover, nanocarriers are essential to combat tumor resistance in various targeting strategies. Nanotechnology may shift the management of HNC through theragnostic approaches, simultaneously allowing diagnosis and therapy. QDs in HNC diagnostics may be useful as they have good optical properties and superior fluo-

rescence intensity. Very limited information is available about the applications of dendrimers in HNC therapy. The contribution of dendrimers for targeted drug delivery in HNC may be more useful. However, for better management of HNC, the NPs' biocompatibility, toxicity, and long-term implications need further trials and understanding before it is applied on a large scale.

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Disclosure of conflict of interest

None.

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Table S1. Chemical agents and their targets in CSCs of HNC

Cetuximab and Erlotinib	EGFR	Decrease percentage of CSCs, induce differentiation.	[1]
Afatinib	EGFR	Afatinib alone or with radiotherapy decreased CSC population.	[2]
	EGFR	Inducing severe apoptosis and an uncommon weak protective autophagic response preferentially in stem-like HNSCC cells.	[3]
ABT-737	Bcl-2	Alone or in combination with radiation, can efficiently eliminate CSCs.	[4]
cetuximab plus ABT-199 with fractional irradiation	EGFR/Bcl-2	The combination significantly inhibited proliferation, invasion/migration, and resistance to apoptosis of HNSCC CSCs in vitro and strongly reduced the tumor growth and increased in vivo survival without side effects.	[5]
C1632 and metformin	Lin28	The combined treatment exerts synergistic anti-tumor effects in OSCC cell lines and xenograft tumor growth in vivo.	[6]
Ibrutinib	BTK	Reduced CSCs number and increase DDP sensitivity of OSCC SP-derived cells.	[7]
CDHP and GSK3β inhibitors	GSK3β	Markedly enhanced 5-FU-induced apoptosis of CD44(high)/ESA(low) cells.	[8]
cisplatin and XAV-939	tankyrase	Synergistically abrogate chemoresistance by increasing DNA damage.	[9]
LF3	Wnt/β-catenin signals	The self-renewal capacity of CSCs was blocked by LF3, as examined by sphere formation.	[10]
sFRP4	Wnt signaling	Decreased expression of CSCs markers (CD44 and ALDH), and inhibit proliferation, EMT and enhanced chemosensitivity of HNSCC CSCs.	[11]
SAHA and TSA	HDAC	Inhibit CSCs marker expression and change stemness genes.	[12]
SAHA	HDAC	Significantly decreased tumorsphere formation of DDP resistant cell lines.	[13]
VPA	HDAC	Inhibit self-renewal, CSC marker expression and potentiated the cytotoxic effect of cisplatin.	[14]
Entinostat	HDAC	Induce cycle arrest (G0/G1 phase), tumor apoptosis and increase in ROS production and significant reductions in CSCs.	[15]
DMF and BSO	GSH	Transient GSH depletion triggered radiation-induced cell death in CSCs.	[16]
UCN-01 and ATRA	Chk1	Decreased the surviving fraction of SQ20B-CSCs after photon irradiation and carbon ions.	[17]
MEDI5117	IL-6	Low dose MEDI5117 decrease CSCs fraction in 3 low-passage patient-derived xenograft (PDX) models of HNSCC, prevented tumor recurrence in a clinical trial.	[18]
PTC209	BMI-1	Enable immune checkpoint blockade to inhibit metastatic tumor growth and prevent tumor relapse by activating cell-intrinsic immunity, in addition to eliminating CSCs.	[19]
celecoxib	COX-2	Suppress messenger RNA expression of stemness-related genes and sphere formation.	[20]

Table S2. Natural products and targets in HNSCC

Compounds of natural herbs	Target point	Effects	Ref
Ovatodiolide (ova)	p-FAK, p-PXN, F-actin, Slug proteins, SOX2, OCT4 and JAK-STAT signaling pathway	Ova inhibited HNSCC tumorsphere formation and attenuated HNSCC stem cell tumorigenicity, inhibited tumor growth.	[21]
Epigallocatechin-3-gallate (EGCG)	Oct4, Sox2, Nanog, CD44, ABCG2 and Notch signaling	EGCG inhibits the self-renewal capacity of HNSC CSCs by suppressing their sphere forming capacity through suppression of Notch pathway.	[22]
quercetin	Twist, N-cadherin, and vimentin	Reduce self-renewal property and stemness signatures expression in head and neck cancer-derived sphere cells.	[23]
A new gamboge derivative compound 2 (C2)	CD49f, CD133, CD44, Ki-67, phosphor-EGFR, CD49f and CD133	Effectively suppresses the growth of CSCs and the formation of tumor spheres.	[24]
Cucurbitacin I	STAT3, JAK2, Bcl-2, Bcl-xL, and survivin	Can effectively inhibit the expression of p-STAT3 and capacities for tumorigenicity, sphere formation, and radio resistance in HNSCC-CD44(+) ALDH1(+).	[25]
YMGKI-1 and YMGKI-2	STAT3 and Src, phosphor-mTOR, HER2, phosphor-EGFR, Phosphatidylinositol 3-kinases (PI3K), phosphor-p44/42 MAPK (Thr202/Tyr204), and phosphor-AMPK	Inhibited stemness (specifically to HNSCC CSCs), decreased expression of CSC markers and promoted radiosensitivity of HNSCC CSCs.	[26, 27]
Plumbagin	Multiple targets (seen in ref)	Inhibit stemness, EMT and induce MET.	[28]
SVC112	Myc, Cyclin D1, Myc and Sox2. SVC112	Inhibits tumor sphere growth in vitro, decrease CSCs number in vivo.	[29]
Lovastatin	CD44, SOX2, c-Myc, CBFb, and Snail	Inhibit CSCs properties and enhance sensitivity of CSCs to therapy.	[30]
Tetrandrine	upregulating Bax and caspase-3 and downregulating Bcl-2	Inhibited the viability of CD133 Hep-2 cells.	[31]
Isoliquiritigenin	ALDH1, CD44, ABCG2, GRP78	Hinder self-renewal, decrease activity of ALDH1 and CD44.	[32]
sulforaphane	SHH, SOX2 and OCT4	SF inhibit HNSCC-CSC viability alone or combined with CIS or 5-FU.	[33]
Liposome encapsulated curcumin-difluorinated (CDF)	CD44	Liposome encapsulated CDF inhibit $CD44^{hi}$ CSCs growth in vitro and vivo.	[34]
Curcumin and metformin		Inhibited the migratory and self-renewal properties of CSCs.	[35]
Isoorientin	p-STAT3, Wnt/β-catenin, p-GSK3, TCF1/TCF7 and LEF1	Targeting OSCC-SC-mediated stemness via blocking Wnt/β-catenin/STAT3 axis.	[36]
Apigenin	CD44, NANOG, and CD105	Down-regulate expressions of CSCs markers, CD44, NANOG, and CD105 of HNSCC cells and the number of cells expressing CSCs markers under hypoxia.	[37]
Resveratrol	ALDH1, CD44, Oct4, Nanog, and Nestin	Reduced CSCs properties in vitro and in vivo via regulating CSCs markers, stemness-related gene signatures and EMT markers.	[38]
silibinin	miR-494-inhibiting Bmi1/ADAM10 expression	Reduced CSCs stemness via activation of miR-494-inhibiting Bmi1/ADAM10 expression.	[39]
Propolis		Reduce CSCs numbers and decrease CSCs markers specifically.	[40]

Table S3. HNSCC markers

Factor	Sample	Identification of HNSCC CSCs	Pathways	Effects	Ref
PI3K	cells derived from HNSCC patient-derived xenografts (PDXs)	by marker (ALDH and CD44)	PI3K upregulates SOX2, SOX2 activate ALDH1A1 and induce CDH1.	CSCs (HPV-positive and HPV-negative) are resistant to standard therapy but are particularly susceptible to PI3K inhibition.	[41]
	Human OSCC cell lines	G0-like OSCC cells		Regulate transition of JARID1B+ CSCs to G0-like cells.	[42]
Hyaluronan (HA)			HA/CD44 signaling.	Stimulate a variety of CSC functions including self-renewal, clone formation and differentiation.	[43]
	Tumor-derived HSC-3 cell line	By marker (ALDH and CD44)	Stimulates the CD44v3 (an HA receptor) interaction with Oct4-Sox2-Nanog leading to both a complex formation and the nuclear translocation of three CSC transcription factors. Suppression of several epigenetic regulators (AOF1/AOF2 and DNMT1) and the up-regulation of several survival proteins (cIAP-1, cIAP-2, and XIAP) leading to self-renewal, clonal formation, and cisplatin resistance by miR-302.	The acquisition of cancer stem cell properties, including self-renewal, clonal formation, and chemotherapy resistance in HA-CD44v3-activated head and neck cancer.	[44]
Snail	HNSCC cell lines	by marker (ALDH and CD44)		Snail-induced EMT gained CSC-like phenotype and was associated with increased chemoresistance.	[45]
	HNSCC cell lines	by marker (ALDH and CD44)/sphere formation	snail.	Induce EMT, chemoresistance and invasive ability and maintained the CSC-like phenotype.	[46]
	Tongue squamous cell carcinoma cell lines	Colony-forming assay/by CSC marker		Induce EMT and promote CSC-like traits.	[47]
	NPC cell lines	by marker CD44 and CD133, sphere formation		Snail mediated a CSC-like phenotype.	[48]
HPV16	HPV-negative OSCC cell lines	Sphere formation/by marker ALDH1+	HPV16/miR-181a/d axis.	Increase self-renewal and enhance CSC-related factor expression.	[49]
	HNSCC cell lines	by marker (CD44high and EpCAMlow)	miR-1281 and miR3194-5p.	HPV16-E6E7 lead to an increase of the migratory CSCs.	[50]
	Human HPV-negative and -positive HNSCC cell lines	Cells with low proteasome activity (expressing the C-terminal degron of murine ODC (cODC) fused to a green fluorescent protein)		RT can dedifferentiate HNSCC cells into CSCs; and radiation-induced dedifferentiation depends on the HPV status of the tumor.	[51]
MELK	HNSCC cell lines	sphere formation	MELK inhibition downregulates SOX2.	MELK plays a key role in CSCs property through the regulation of SOX2.	[52]
Renin-angiotensin system (RAS)	MDHNCSCC tissue samples and MDHNCSCC-derived primary cell lines	by stemness-related gene expression		RAS are expressed by the oct4+ and SOX2+ cells within the tumor nests (TNs) and the peritumoral stroma (PTS).	[53]
	buccal SCC tissue samples and -derived primary cell lines	by stemness-related gene expression		RAS are expressed by the oct4+ and SALL4+ in buccal SCC within the tumor nests (TNs) and the peritumoral stroma (PTS).	[54]
	MDOTSCC tissue samples	IHC staining for stemness-related gene expression		expression of components of the RAS by the CSC subpopulations within MDOTSCC.	[55]
	MHNCSCC tissue samples and MHNCSCC-derived primary cell lines	SOX2+ cells as CSCs		Expression of components of the RAS by the CSC subpopulations within MHNSCC.	[56]

SPLUNC1 and MLL3	NPC mouse model using C666-1 cells	by SOX2 expression	Downregulated expression of SPLUNC1, increased expression of MLL3.	Downregulated expression of SPLUNC1, increased expression of MLL3 is corrected with stage of NPC.	[57]
XIAP	Human NPC S-18 and S-26 cell lines	SP cells; CD44+ cells; by stemness-related gene expression	Blocked autophagic degradation of Sox2 by inhibiting ERK1 activation in CSCs, positively correlated with Sox2 expression.	Maintain CSCs, antagonist of IAPs combined with DDP/5-FU exerted antitumor effect on CSCs.	[58]
BMI1	HNSCC induced from mouse model, HNSCC cell lines	BMI+ HNSCC cells	BMI increased AP-1 activities.	BMI1+ CSCs drives invasive growth and metastasis of HNSCC, Inhibiting AP-1 or BMI1 sensitized tumors to DDP, and eliminated lymph node metastases.	[59]
	HNSCC tissue samples, laryngeal Hep-2 cell lines	by marker CD133		BMI1 was required to maintain the proliferative capacity of laryngeal CD133 CSCs.	[60]
p38 MAPK	HNSCC tissue samples, cell lines	by CSC marker SOX2, Oct4, Klf4, c-Myc and CD44		p38 MAPK activation may play a role in therapeutic resistance and disease relapse in HNSCC by maintenance of CSCs phenotype.	[61]
Wnt/β-catenin	HNSCC cell lines, primary HNSCC tissues	by marker (ALDH and CD44)/sphere formation	β-catenin directly regulates Oct4 transcription in HNSCC stem-like cells.	Maintains self-renewal and tumorigenicity of head and neck squamous cell carcinoma stem-like cells.	[62]
SOX8	Cisplatin-resistant tongue squamous cell carcinoma (TSCC) cells lines	Sphere formation/by stemness-related gene expression	SOX8 could bind to the promoter region of FZD7 and activated FZD7-mediated Wnt/β-catenin pathway.	Induce chemoresistance, stem-like properties and EMT.	[63]
SOX2	HNSCC cell lines, Primary sphere cells from surgical specimens from HNSCC patients	by CSC marker/sphere formation/by stemness-related gene expression	Induce ABCG2, snail, cyclin B1 expression.	SOX2 enhanced stemness and enhance chemoresistance of CSCs.	[64]
RARS-MAD1L1	NPC cell lines	SP cells, by stemness-related gene expression	RARS-MAD1L1 interacted with AIMP2, which resulted in activation of FUBP1/c-Myc pathway.	RARS-MAD1L1 might contribute to tumorigenesis, CSC-like properties, and therapeutic resistance.	[65]
LIN28B	Dissociated cells derived from the samples of OSCC patients	by marker (ALDH and CD44)/sphere formation	ARID3B and HMGA2 as direct targets of LIN28B/Let7, mediating Oct4 and Sox2 expression by direct regulation of Oct4 and Sox2 promoter activity, respectively.	Lin28B(HIGH)/Let7(LOW) regulates key cancer stem-like properties in oral squamous cancers.	[66]
HSP90	HNSCC cell lines	by marker (ALDH and CD44)/sphere formation		HSP90 inhibitor decrease CSC stemness.	[67]
5T4	HNSCC cell lines	by marker (ALDH and CD44)		5T4 is more highly expressed in head and neck CSC, inhibitor caused a significant reduction in the CSC fraction.	[68]
c-Met	Cell lines from HNSCC tumor tissue	by marker (ALDH and CD44)/sphere formation/SP cells/by stemness-related gene expression		c-met upregulate ALDH1 and ABCG2 activity and associated with stemness as well as chemoresistance.	[69]
	Cell lines were obtained at the primary surgery before any treatment	Mouse HNSCC xenograft model/sphere formation	Increased expression of self-renewal pathways.	c-Met could serve as a novel single marker for CSCs at least in HNSCC.	[70]
	Single-cell suspensions derived from primary specimens	by CSC marker (c-Met and CD44)	Due to downregulation of Wnt/β-catenin signaling in HN-CSC and that the Wnt pathway receptor FZD8 was essential for interactions of c-Met and Wnt/β-catenin signaling in HN-CSC.	Silencing c-Met is sufficient to suppress sphere formation, tumor initiation, and metastatic properties of HN-CSC.	[71]
MACC1	HNSCC cell lines	by marker ALDH1		MACC-1 gene overexpress in CSCs compared with cancer cells.	[72]

The Hippo-TAZ	HNSCC cell lines	by marker (CD133 and CD44)/stemness-related gene expression	SOX2 as a putative downstream target of TAZ.	Promote CSCs maintenance and tumorigenicity in HNSCC.	[73]
	OSCC cell lines	the colony formation, tumorsphere assays, by marker CD44 and CD133	TAZ-TEADs binding and subsequent transcriptional activation of EMT mediators and pluripotency factors are presumably responsible for TAZ-mediated EMT and non-CSCs-to-CSCs conversion.	TAZ is required for oral CSCs self-renewal and maintenance and endow non-CSCs with CSCs-like traits.	[74]
Oct-4	Cell lines from HNSCC tumor tissue	by CSC marker		Oct-4a is a stemness marker and oct-4a+ cells have ability of chemoresistance.	[75]
	HNSCC cell lines	by marker (ALDH and CD44)/sphere formation/SP cells	Regulate the cell cycle checkpoint kinases CHK1 and WEE1 and homologous recombination (HR) repair genes PSMC3IP and RAD54L.	Loss and overexpression of Oct4 may lead to tumor cell radio sensitization, Oct4-regulated genes contribute to the HNSCC radio resistance by modulating the DNA repair and CSC properties.	[76]
RXRα	hep-2 and fadu cells	by marker (CD133 and CD44)/sphere formation/SP cells/by stemness-related gene expression		Overexpression of RXRα was able to expand the CSC-like properties in HNSCC cells.	[77]
IGF-R and EGFR	Cell lines were obtained at the primary surgery before any treatment	Sphere formation/by marker (ALD)		Using specific inhibitors against EGFR and IGF-1R reduced stem cell fractions drastically.	[78]
EGFR	Tongue epithelial squamous cell carcinoma cell line	Sphere formation	SOX2 was a binding partner and substrate of EGFR.	EGFR plays an important role in the development of cancer stem cells.	[79]
	HNSCC cell lines	by marker (CD44)/sphere formation/by stemness-related gene expression	The induction of CD44, BMI-1, Oct-4, NANOG, CXCR4, and SDF-1.	EGFR plays critical roles in the survival, maintenance, and function of cancer stem cells.	[80]
Notch1	HNSCC cell lines	by CSC marker/sphere formation/by stemness-related gene expression	Notch1 acted upstream of canonical Wnt signaling in HNSCC cells and regulate CSCs markers as well as ABC transporters.	Notch1 signaling contributes to stemness.	[81]
	HNSCC cell lines CAL27 and FaDu, Human HNSCC tissue	by self-renewal-related markers, CD44, BMI1, SOX2, ALDH1, and Slug/sphere formation/by marker (CD44 CD133)		NOTCH1 is associated with CSCs in HNSCC tissue and NOTCH1 inhibition delays tumorigenesis and effectively reduces CSC self-renewal of nude mice HNSCC xenograft. Furthermore, chemotherapeutically combined NOTCH1 inhibitor synergistically attenuated chemotherapy-enriched CSC population in vitro and in vivo, which provides the possibility to effectively eliminate head and neck CSCs.	[82]
	TSCC cell lines	by marker (ALDH1, CD133 and CD44)/sphere formation		NOTCH1 is required for stemness of TSCC tumor cells.	[83]
DOT1L	Tumor-derived HSC-3 cell line (isolated from human squamous carcinoma cells of the mouth)	by marker (ALDH and CD44)	Histone methyltransferase, DOT1L-associated epigenetic changes induced by HA play pivotal roles in miR-10 production leading to up-regulation of RhoGTPase and survival proteins.	Acquisition of cancer stem cell properties including self-renewal, tumor cell invasion, and chemotherapy resistance.	[84]
NLRP3 inflammasome	SCCHN cell lines	by marker (BMI1, ALDH and CD44)/sphere formation/by stemness-related gene expression	Activated by LPS and ATP and upregulate of BMI1, ALDH1 and CD44.	CSCs self-renewal activation in SCCHN.	[85]
TRAF6	HNSCC cell lines	by EMT marker (Vimentin and Slug) and CSC marker (CD44, ALDH1, KLF4, SOX2 and AGR2)/sphere formation	Associated with CD44, ALDH1, KLF4 and SOX2 expression, the anchor-dependent colony formation number and sphere number formed.	TRAF6 plays a role in EMT phenotypes, the generation and maintenance of CSCs in SCCHN.	[86]

GRP78	HNSCC cell lines	by marker (CD133, ALDH and Cripto-1)/sphere formation/SP/by stemness-related gene expression		Induce self-renewal ability, side population cells and expression of stemness genes.	[87]
	HNSCC cell lines	CD24(-) CD44(+) cells	Regulating CSC related factors (Oct-4 and Slug) and EMT related factors (CK18 and involucrin).	Grp78 regulated the conversion of CD24(-) CD44(+) cells, a characteristic of HNC stem cells.	[88]
S100A4	HNSCC cell lines	Sphere formation	Mediated by repressing p53 and subsequently activating the Nanog expression.	Both the calcium-binding ability and the C-terminal region of S100A4 are important for HN-CICs to sustain its stemness property and malignancy.	[89]
	HNSCC cell lines	Sphere formation/SP cells	Induce Notch2 and PI3K (phosphoinositide 3-kinase)/pAKT.	Maintaining the stemness properties and tumorigenicity of CSCs.	[90]
RhoC	HNSCC cell lines derived from patients with T2N0 of floor of the mouth and T3N1 of base of the tongue respectively	by marker (ALDH and CD44)/sphere formation	by overexpressing IL-6 and phosphorylation of STAT3.	Regulation and activation of stem cell transcription factors.	[91]
GSK3β	SCC cell lines	Sphere formation/by marker CD44 and ESA	Regulate Oct4, Sox2, and Nanog and reversely regulate Calgranulin B and Involucrin.	Maintenance of stem cell self-renewal.	[92]
c-Fos	HNSCC cell lines	Sphere formation	Increased the expression of pERK and cyclin D1.	Enhanced the epithelial-mesenchymal transition (EMT) state and expression of CSC markers (Nanog, c-Myc, Sox2, and Notch1).	[93]
G9a	HNSCC cell lines	by marker (CD44)/sphere formation	Interacts with Snail and mediates Snail-induced transcriptional repression of E-cadherin and EMT, through methylation of histone H3 lysine-9 (H3K9).	EMT-mediated metastasis and maintenance of cancer stem cell-like characters.	[94]
HDAC	HNSCC cell lines	by marker (ALDH)/sphere formation		Inhibition of HDAC may constitute a novel strategy to disrupt the population of CSC in head and neck tumors to create a homogeneous population of cancer cells with biologically defined signatures and predictable behavior.	[95]
SASP	Mouse model	by CSC marker	The effects of chemokines were primarily mediated by PI3K signaling.	The telomere DDR regulates senescence-associated paracrine interactions between cancer stem cell populations, dramatically affecting tumor progression and metastasis.	[96]
sLeX	Primary and metastatic HNSCC cell lines	by marker (ALDH and CD44)/sphere formation		sLeX relationship with CSC in HNSCC.	[97]
fucosylation	HNSCC cell lines	sphere formation	Fucosyl-transferases FUT3 and FUT6 highly up-regulated, increased SLex expression and increased adhesion by shear flow assays in orospheres.	Fucosylation function to spheres formation, fucosylation is of paramount importance in the invasion and metastatic process of CSCs.	[98]
CD200	HNSCC tumor cell lines	by stemness-related gene expression (shh and BMI1)	CD200 was diversely expressed and consistently associated with expression of Bmi-1 and Shh. Overexpression of CD200 induced Bmi-1 and Shh.	CD200 was related to CSC features.	[99]
CK2	HNSCC tumor cell lines	SP cells/by stemness-related gene expression (Nanog, Oct4 and Sox2)/sphere formation	CK2 is associated with stem cell gene.	Aberrant CK2 signaling inhibits TAp73 to promote the expression of CSC genes and phenotype.	[100]
CD10	HNSCC tumor cell lines	by marker (ALDH, CD133 and CD44)/sphere formation/by stemness-related gene expression (OCT3/4)	CD10-positive subpopulation expressed the CSC marker OCT3/4 at a higher level, CD10-positive subpopulation was more refractory to cisplatin, fluorouracil and radiation.	CD10 is associated with therapeutic resistance and CSC-like properties of HNSCC.	[101]

SDF-1α/CXCR4	HNSCC tissue	by marker CD44		SDF-1-CXCR4 axis may play an important role in the cancer stem cell theory of HNSCC.	[102]
PinX1	Nasopharyngeal cancer cell line CNE2	by CSC marker (CD133)	Possibly through TRF1, Mad1/c-Myc, and p53-mediated pathways.	PinX1 downregulates telomerase activity in $CD133^+$ CSCs, inhibits its proliferation, migration, and invasion, and induces apoptosis.	[103]
	Nasopharyngeal cancer cell line CNE2	by CSC marker (CD133)	by regulating the P53/miR-200b-mediated transcriptional suppression of Snail1, Twist11, and Zeb1.	Overexpression of PinX1 and P53 could inhibit nasopharyngeal $CD133^+$ CSC proliferation, migration, and invasion.	[104]
SMURF1	HNSCC cell lines	Sphere formation/by marker (ALDH and CD44)	Inhibition of BMP signaling potentiates the long-term survival of HNSCC CSCs.	The maintenance and progression of CSCs.	[105]
PLOD2	FaDu and Hep2 cell line	Sphere formation/by marker (CD133 and CD44)/SP cell	Activate Wnt pathway.	PLOD2 contributes to the CSC-like properties of Hep-2 and FaDu cells.	[106]
GLI3	Tongue squamous cell carcinoma cell lines	by marker CD44	*GLI3* gene silencing resulted in a significant decrease in *CD44*, *BMI1*, *POU5F1* (*OCT4*) and *SNAI2* (*SLUG*), IVL and S100A9 (Calgranulin B).	GLI3 contributes to OSCC stemness and malignant behavior.	[107]
ZEB1/ZEB2	Cell lines from HNSCC tumor tissue	by marker CD133		CSC-like properties, including self-renewal ability, the expression of stemness markers, and drug resistance.	[108]
Id2	HNSCC cell lines	Sphere formation/by marker (CD44)/ by stemness-related gene expression		Id2 associated with stemness of HNSCC cells.	[109]
BMP4	OSCC cell lines	by EMT and stemness-related gene expression (E-cadherin, Snail, Slug, Bmi-1, CD44, hTERT)	Regulation of CSC markers.	BMP-4 (bone morphogenetic protein-4) could induce epithelial-mesenchymal transition (EMT) with acquisition of stem cell-like phenotypes in a cell-culture model.	[110]
ISG15	NPC cells lines	The colony formation, tumor sphere assays, by stemness-related gene expression (BMI1, c-MYC, NANOG, and KLF4)	Expression levels of pluripotency-associated genes, including BMI1, c-MYC, NANOG, and KLF4 increased.	ISG15 promotes CSC phenotype and radiation and chemotherapy resistance in NPC.	[111]
EVI1	NPC cell lines	SP, sphere formation, by marker PKH26+ and ALDH1+, by stemness-related gene expression (SOX2, Nanog, c-Myc, and Oct4)	EVI1, snail, and HDAC1 formed a co-repressor complex to repress E-cadherin expression; EVI1 directly bound at β-catenin promoter and activated its expression.	β-catenin mediated EVI1's function on cancer stem cells (CSCs) properties: the sphere formation ability and the pluripotent transcription factors (SOX2, Nanog, c-Myc).	[112]
STAT3	HNSCC cell lines	by self-renewal-related markers, ALDH1, CD44, OCT4 and SOX2/ sphere formation		p-stat3 corrected with CSC property.	[113]
Skp2	NPC cell lines AND NPC specimens	by marker ALDH1 and sphere formation		Knockdown of Skp2 partially reduced cell proliferation, promoted cellular senescence, and decreased the population of stem cell like aldehyde dehydrogenase 1 positive NPC cells as well as their self-renewal ability.	[114]
LMP2A	NPC cell lines AND NPC specimens	by stemness-related gene expression (BCG2, Bmi-1, Nanog, and SOX2)/SP cells/sphere formation	Regulate Akt activity.	LMP2A induces EMT-like cellular marker alteration and strongly up-regulates the cancer stem cell-like population in NPC.	[115]
OLFM4	HNSCC cell lines	OLFM4 is a stem cell-related gene	Regulated by aberrant DNA methylation.	The aberrant stemness gene OLFM4 expression caused by altered DNA methylation appeared to regulate early-stage HNSCC characteristics.	[116]

topoisomerases	OSCCs tissue	by marker CD44 and CD24		All topoisomerases correlate with OSCC CSCs.	[117]
mTOR signaling pathway	NPC cell lines	by marker CD44, sox2 and OCT4	Downregulating the expression of CD44, SOX2 and MMP-2.	mTOR signaling plays significant roles both in maintaining NPC CSCs and in cancer progression.	[118]
JARID1B	Human OSCC cell lines	Sphere formation		JARID1B knockdown inhibit CSCs activity and reduced mRNA levels of NQO1, KEAP1, NRF2, FOXO1, FOXO3, KLF4, OCT4, CD133, and Nanog with radiotherapy.	[119]
Slug	HNSCC cell lines	Sphere formation/by marker CD44 and ALDH/SP cells/by stemness-related gene expression		Slug expression corrects with self-renewal capacity, stemness-associated gene expression, and cisplatin chemoresistance.	[120]
CCL21/CCR7	OSCC cell lines	by stemness-related gene expression (CD133, CD44, ALDH1A1, OCT4, BMI1, BCG2, Bmi-1, Nanog, and SOX2)/sphere formation	By activating the JAK2/STAT3 signaling pathway.	CCL21/CCR7 axis regulated EMT progress and promoted the stemness of OSCC.	[121]
MTA3	TSCC cell lines	by marker ALDH1	Negatively correlated with SOX2.	MTA3 is capable of repressing TSCC CSC properties and tumor growth.	[122]
CMTM6	HNSCC cell lines	by marker ALDH1, CD44 and BMI1, and sphere formation	A significant positive correlation between expression of *CMTM6* and EMT- and CSC-related genes, immune checkpoint components.	CMTM6 regulates stemness, EMT, and T-cell dysfunction.	[123]
PIK3CA	HNSCC cell lines	by marker CD44, CD24low and ALDH1/SP/sphere formation	Activate Ephs, TRKs and the c-Kit pathway.	Promotes CSC population.	[124]
	a mouse model	CSCs derived from HNSCC of mouse		Hyper-activation of PIK3CA and loss of p53 in stem cells lead to the spontaneous development of multilineage of tumors with immunosuppressive TME.	[125]
SFRP1	Cell lines from tumor of mouse skin	by marker	Loss of SFRP1 Expression Leads to Upregulation of SOX-2.	Sfrp1 loss results in early tumor initiation and CSC regulation.	[126]
Nrf2	Cell culture from primary HNSCC samples	by marker CD133 and SP	Nrf2 upregulate ABCG2.	Nrf2 mediated drug resistance in HNSCC CSCs.	[127]
Gli1	Tongue squamous cell carcinoma line CAL33	Sphere formation		A CSCs marker.	[128]
CD47-SIRPα	OSCC cell lines	Sphere formation/by stemness-related gene expression CD47, OCT4, SOX2, CD133, and c-MYC	Associated with regulation of CD133, SOX2, OCT4, c-Myc, vimentin, Slug, Snail, E-cadherin and N-cadherin.	Promoted the generation of CSCs and malignant OSCC phenotypes.	[129]
WHSC1	HNSCC cell lines	Sphere formation	WHSC1-mediated H1.4K85 mono-methylation induces transcriptional activation of OCT4.	Enhance stemness features in HNSCC cells.	[130]
ZSCAN4	HNSCC cell lines	by marker CD44 and ALDH1/sphere formation/by stemness-related gene expression (OCT3/4, NANOG, KLF4, BMI1 and SOX2)	ZSCAN4 leads to a functional histone 3 hyperacetylation at the promoters of OCT3/4 and NANOG.	Form tumorspheres and tumor growth.	[131]
xCT	Tissue samples, HNSCC cell lines	by marker CD44	Xct mediated control of redox status in CD44v-expressing cancer cells.	xCT-targeted therapy may deplete CD44v-expressing undifferentiated HNSCC cells and concurrently sensitize the remaining differentiating cells to available treatments including EGFR-targeted therapy.	[132]
RCOR1/MED28	ocscc cell lines		MED28 correlate with CSC-related properties and induce expression of CSCs markers (CD44, KLF4, NANOG, and OCT4).	The effect of MED28 could be abrogated by RCOR1 via direct interaction.	[133]

WNT5A	The NPC line CNE-2 and its clones S18, S22, and S26	by marker CD44high CD24low/SP cells/by EMT marker Vimentin	Activate protein kinase C (PKC) signaling.	Promoted EMT in NPC cells, induced the accumulation of CD24-CD44+ cells and side population.	[134]
AGR2	HNSCC cell line	Sphere formation/by stemness-related gene expression (Nanog, Sox2 and OCT4)/by EMT marker (Slug and Snail)	AGR2 was remarkably correlated with Survivin, Cyclin D1, ALDH1, Sox2, Oct4, and Slug in HNSCC tissue.	AGR2 is involved in EMT and self-renewal of CSC.	[135]
Cathepsins	Tissue samples	by stemness-related gene expression OCT4		Cathepsins B and D were localized to CSCs within the tumor nests, while cathepsin B was localized to the CSCs within the peri-tumoral stroma, and cathepsin G was localized to the tryptase$^+$ phenotypic mast cells within the peri-tumoral stroma.	[136]
CYP1B1	HNSCC cell lines	by stemness-related gene expression (OCT4, NANOG, KLF4, BMI1, ALDHA1)/by marker ALDH		CYP1B1 is crucial for stemness.	[137]
VAV2	hnSCC (tongue-located) patient-derived cells	by stemness-related gene expression		VAV2-regulated stem cell-like (SCL) program does harbor a number of cell cycle- and signaling-related kinases, VAV2-regulated SCL gene signature is associated with poor hnSCC patient prognosis.	[138]
TSPAN1	HNSCC cell lines		Correlated with EMT features and SRC activation.	Increase in resistant cells, and is associated with proliferation, resistance, metastasis, survival of resistant cells.	[139]
TrkB	Laryngeal cancer cell lines Hep-2, TU177, TU686, and AMC-HN-8	Sphere formation/by marker (CD44)/ by stemness-related gene expression (SOX2 and OCT4)	miR-10a-5p Regulated TrkB Expression by Interacting with 3'-UTR of BDNF.	TrkB induce cancer stem cell-like property, miR-10a-5p inversely regulate TrkB expression.	[140]
PGK1	Patients and tissue samples, OSCC tumor cell lines	Sphere formation/by stemness-related gene expression (Sox2, Oct4 and Nanog)	Through the AKT signaling pathway.	PGK1 expression and glycolysis whilst activating the characteristics of oral cancer stem cells and EMT under hypoxia.	[141]
IGF-1	OSCC cell line SCC-4	Sphere formation/by marker CD44	IGF-1-mediated regulation of AKT and HH pathways.	IGF-1 exerts pro-tumorigenic effects by stimulating SCC-4 cell proliferation, migration, invasion and stemness.	[142]
super-enhancers (SEs)	HNSCC cell lines	by marker CD44, EpCAM and ALDH/ sphere formation	FOSL1, BRD4 recruit mediators to establish SEs at a cohort of cancer stemness and pro-metastatic genes.	FOSL1 and BET inhibitors disrupting SEs inhibit CSCs and eliminate CSCs, furtherly inhibit tumor growth and metastasis.	[143, 144]
HOXA10-AS	OSCC cell lines	by marker CD133, CD44/sphere formation	Through the miR-29a/MCL-1/PI3K/AKT axis.	HOXA10-AS enhances the stem cell property of OSCC stem cells.	[145]
HSD17B7	Patients' samples and HNSCC cell lines	Sphere formation	High expression in many genes of the signature related to cellular respiration, electron transport chain, and mitochondrial organization and biogenesis.	Involve in stem self-renewal and tumorigenicity of primary keratinocytes (HKCs) and SCC cells.	[146]
PGE2	HNSCC cell line	by marker CD44 and ESA	PGE2-induced NR4A2 expression.	CD44high/ESAlow CSCs produce PGE2 to compromise 5-FU induced apoptosis to CD44high/ESAhigh cells.	[147]
Cancer associated fibroblast/wnt	Cell lines from HNSCC tumor tissue	by marker (ALDH and CD44)/sphere formation	Cancer associated fibroblast activate and regulate wnt signaling withnin cancer cells.	Wnt in cancer cells and the tumor epithelial-stromal boundary is enssential in CSCs property.	[148]
cancer associated fibroblast/PTK7	HNSCC cell lines	by CSCs marker/sphere formation	CAF-derived POSTN activate PTK7-Wnt/β-Catenin signaling activation.	Promote cancer stemness.	[149]

Cancer-Associated Fibroblasts (CAFs)	HNSCC cell line	Sphere formation/by stemness-related gene expression ALDH1, NANOG, SOX2, OCT4, ABCG2, CD44, CD133, and Nestin	Factors secreted by CAFs activate EGFR, IGFR, and PDGFR Signaling.	Induced the expression of stemness-related genes and sustain cancer stem properties.	[150]
hypoxia	Human laryngeal cancer cell lines, Hep-2 and AMC-HN-8	by marker CD133	Upregulated stem-related gene expression.	Upgrade the stem-like biological properties of laryngeal cancer cell lines by increasing the CD133+ stem cell fraction.	[151]
TAM markers	OSCC tissue	by marker (SOX2, ALDH1, and CD44)		TAM markers are associated with cancer stem cell marker and OSCC overall survival.	[152]
IL-6	HNSCC cell lines	by marker (ALDH and CD44)		Endothelial cell-secreted IL-6 induce HNSCC CSCs migration, EMT and maitain CSCs.	[153]
IL-6	Low-passage patient-derived xenograft (PDX) models of HNSCC			IL-6 enhances the survival and tumorigenic potential of head and neck cancer stem cells.	[36]
IL-6	Single-cell suspensions derived from primary specimens	by marker (ALDH and CD44)/sphere formation	IL-6 induces STAT3 phosphorylation.	Endothelial cell secreted-IL-6 signaling promotes self-renewal and survival of human primary head and neck cancer stem-like cells.	[154]
IL-4	Cell culture from primary HNSCC samples	by marker CD133 and SP cells		Autocrine IL-4 from CD133 SP cells promote multidrug and apoptosis resistance.	[155]
IL-1β	Mouse SCC cell lines	Sphere formation/by CSC marker/by stemness-related gene expression	Activate Smad/ID1 signal pathway.	Promote the stem-like capabilities of HNSCC cells.	[156]
EGF	HNCSS cell lines	by CD44 and EMT regulators and stemness-related gene expression	EGFR/PI3K/HIF-1α axis-orchestrated glycolysis.	EGF induces EMT and enrichment of CSCs.	[157]
TGFβ	HNSCC K3 CSCs	The CSC properties of the cell line have been validated	TGFβ1 induce Oct4, Sox2, ABCG2, Twist, Snail, Slug and Wnt/β-catenin signaling.	Increase EMT, self-renewal capacity and chemoresistance to cisplatin of HNSCC CSCs.	[158]
Chewing Tobacco	Het1A, a non-neoplastic and non-transformed epithelial cell line from the human esophagus	by marker (ICAM1 and CD44)		Chronic Exposure to Tobacco Extract lead to elevated expression of several ESCC cancer stem cell markers.	[159]
Arecoline-exposure	Gingival epithelial and FaDu OSCC cell lines	by marker (ALDH and CD44)/sphere formation/by stemness-related gene expression	Down-regulation of miR-145.	Chronic arecoline exposure induces malignant phenotype with the acquisition of cancer stemness/EMT, and oncogenicity.	[160]
Nicotine	HNSCC cell lines	Sphere formation/by stemness-related gene expression (CD44, Bmi1, Oct4, Nanog)	by repressing E-cadherin expression and led to the induction of stem cell markers Oct-4, Nanog, CD44 and BMI-1, the upregulation of miR-9, a repressor of E-cadherin, and the downregulation of miR-101, a repressor of EZH2.	Regulating cancer stem cell characteristics.	[161]
Cigarette smoke	HNSCC cell lines	SP cells	via Akt-mediated regulation of ABCG2 activity.	Increased the size of the side population (SP).	[162]
lower level of miR-204	HNCSS cell lines	ALDH1+, SP, and sphere forming OSCC cells/sphere formation	miR-204 binds on their 3'UTR-regions of Slug and Sox4 for an inhibitive role.	Down-regulation of miR-204 significantly increased cancer stemness and the lymph nodes incidence of orthotopic animal models.	[163]
miR34a	HNSCC cell lines	by marker (ALDH)/sphere formation	MiR-34a reversely regulate EMT- and CSCs related transcription factors.	Upregulation of miR 34a significantly inhibited the capability for EMT formation of CSC-phenotype and functionally reduced clonogenic and invasive capacity.	[164]
MicroRNA-200c	Cell lines from HNSCC tumor tissue	by marker (ALDH and CD44)	by reducing the expression of BMI1/ZEB1, Snail and N-cadherin.	Negatively modulates the expression of BMI1 but also significantly inhibits the metastatic capability of epithelial-mesenchymal transitions.	[165]

MiR-520b	HNSCC cell lines	Sphere formation	Inhibit CD44 and multiple stemness regulators expression.	Suppressed spheroid cell formation in vitro, restrained tumorigenesis in vivo.	[166]
MicroRNA let-7a (low expression)	Cell lines from HNSCC tumor tissue	by marker ALDH1	let-7a inversely regulate CSCs related gene.	Plays a role in eliminating the putative HNSCC CSC population.	[167]
Let-7c	OSCC cell lines	by marker (ALDH1 and CD44)/sphere formation	let-7c-IL-8 pathways.	Ectopic expression of let-7c in CSCs down-regulated the stemness hallmarks and the radio/chemoresistance.	[168]
lncRNA-PVT1	NPC cell lines	Sphere formation/by marker (CD24 and CD44)/by stemness-related gene expression (Oct4, c-Myc, SOX2, ALDH1)	via inhibiting miR-1207 and activating the PI3K/AKT signal pathway.	Pvt1 promotes cancer stem cell-like properties in NPC cells.	[169]
LINC-PINT (low expression)	Human type-2 epithelial cells (Hep-2)	Sphere formation	miR-425-5p/PTCH1/SHH axis.	Downregulation of LINC-PINT was associated with increased laryngeal cancer stemness and chemoresistance to cisplatin.	[170]
miR-125a/HAX-1	Laryngeal Hep-2 cell lines	by CSC marker CD133	miR-125a inhibit HAX-1.	Low miR-125a expression lead to Hep-2 CSCs chemoresistance.	[171]
LINC00963	OSCC cell lines	by marker CD44 and ALDH1 and sphere formation	Positively correlated with the expression of the cancer stemness markers (Sox2 and CD44) and drug resistance markers (ABCG2 and ABCB5).	The downregulation of LINC00963 inhibited CSC hallmarks: elf-renewal, invasion and colony formation ability.	[172]
miR-495 (low)	Cell lines from OSCC tumor tissue	by marker (CD133 and CD44)/sphere formation	miR-495 could inhibit the activation of the TGF-β signaling pathway and HOXC6.	miR-495 may suppress HOXC6 to inhibit EMT, proliferation, migration, and invasion while promoting apoptosis of CSCs in OSCC by inhibiting the TGF-β signaling pathway.	[173]
miR-1246/CCNG2	HNSCC cell lines	by marker CD44, cd133 and ALDH1 and sphere formation	Repression of CCNG2 and induction of ABCG2.	Induce stemness, modulate chemoresistance.	[174]
MicroRNA-134	OSCC cell lines	by marker CD44, CD133	MicroRNA-134 mediate LAMC2 downregulation to suppressing PI3K-Akt signaling pathway.	Inhibit migration and invasion of OSCC CSCs.	[175]

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