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# Biology and immunology of cancer stem(-like) cells in head and neck cancer

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## Contents



## Abstract

Immunological approaches against tumors including head and neck squamous cell carcinoma (HNSCC) have been investigated for about 50 years. Such immunotherapeutic treatments are still not sufficiently effective for therapy of HNSCC. Despite the existence of immunosurveillance tumor cells may escape from the host immune system by a variety of mechanisms. Recent findings have indicated that cancer stem(-like) cells (CSCs) in HNSCC have the ability to reconstitute the heterogeneity of the bulk tumor and contribute to immunosuppression and resistance to current therapies. With regard to the CSC model, future immunotherapy possibly in combination with other modes of treatment should target this subpopulation specifically to reduce local recurrence and metastasis. In this review, we will summarize recent research findings on immunological features of CSCs and the potential of immune targeting of CSCs.
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*Keywords:* Cancer stem cells; ALDH1; Epithelial–mesenchymal transition; Human papillomavirus; Immunotherapy; Vaccination

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## 1. Introduction

The current treatments for head and neck squamous cell carcinoma (HNSCC) have been challenged by the cancer stem(-like) cell (CSC) hypothesis. These cells play a central role in initiation, progression, invasion, metastasis, recurrence of tumors and resistance to therapies [1]. *In vitro* and *in vivo* studies of HNSCC have shown that putative CSCs or CSC-enriched non-adherent spheroid cells present with stem cell-like self-renewal properties, invasion capacity and therapy resistance [2–5]. The CSC model is closely related to the phenomenon that HNSCC initially respond well to conventional treatments, but local and distant relapses occur frequently. It is interesting to note that phenotypic heterogeneity and plasticity of CSCs was observed to be associated with epithelial-mesenchymal transition (EMT), which collectively promotes metastasis [6]. Subsequently, CSCs require a special microenvironment to regulate their stemness, and to initiate and promote cancer development by recruiting and activating special cell types [7–10].

The development and the introduction of immunotherapy for HNSCC holds promise as an attractive supplement to traditional treatments such as surgery, chemotherapy, and radiation therapy. Since immunotherapies are designed to target directly the tumor cells the incidence of side effects is expected to be low. Many approaches based on bulk tumor cells have been developed and successfully monitored, but a correlation with good clinical responses has been sparse so far [11,12]. The main issues in developing cancer immunotherapy are the strengthening of cytotoxic T cell responses and prevention or reversal of tumor-induced immune-escape. Emerging evidence indicates that the host immune system is able to recognize CSCs and mount an effector response against them, but CSCs may also play a role in mediating immunosuppression within the tumor microenvironment [13,14]. Therefore, it is necessary to gain further insight into the immunological features of CSCs and explore potential immunotherapeutic approaches against CSCs. In this review, we discuss the biology of CSC in HNSCC with regard to their potential as targets for future immunotherapy.

## 2. The CSC hypothesis in HNSCC

Accumulating evidence suggests that in a heterogeneic tumor, a subpopulation of tumor cells with stem cell-like self-renewal capacity, known as CSCs or tumor-initiating cells (TICs) have the ability to give rise to a proliferative bulk tumor cell mass and to survive systemic treatments [1]. CSCs have been identified in many types of solid tumors including HNSCC [15,16]. One of the first studies of CSCs in HNSCC using an immunodeficient mouse as model demonstrated that a minor population of $CD44^+$ cancer cells, which account for less than 10% of cells in a HNSCC primary tumor, could give rise to new tumors *in vivo* and displayed the ability of self-renewal and differentiation [2]. In consistency with this finding, important advances have been achieved in the study of the role of HNSCC CSCs in the progression of malignancies in *in vitro* or *in vivo* mouse models and patient-derived clinical samples.

### 2.1. CSCs in cancer progression and metastasis

Once initiated, CSCs may generate macroscopic tumors through the stem cell processes of self-renewal and differentiation into multiple cell variants. Furthermore, CSCs may undergo EMT, a process involved in embryogenesis and considered also to be involved in metastatic dissemination [17]. During EMT, cells of epithelial phenotype convert to migratory and invasive cells with mesenchymal phenotype. When the migrating mesenchymal cells have reached their destination, they may undergo a reverse process, a mesenchymal–epithelial transition (MET), to regain the epithelial phenotype. Recent studies highlight that tumor cells undergoing EMT acquire stem cell-like properties, and EMT can also induce non-CSC to acquire a CSC-like state (Fig. 1) [18–20].

We previously showed that aldehyde dehydrogenase 1 $(ALDH1)^+$-CSC enriched cell populations from 3 dimensional spheroid cultures generated from HNSCC cell lines displayed EMT characteristics with enhanced colony forming ability and invasiveness [4]. Further, the presence of HNSCC-CSCs with the ability to undergo both EMT and MET by switching between their epithelial and mesenchymal phenotypes has been discovered by Biddle et al. [6]. Migratory $CD44^{high}$ epithelial-specific antigen $(ESA)^{low}$ EMT-CSC expressed EMT markers and a mesenchymal phenotype, while $CD44^{high}ESA^{high}$ non-EMT-CSC had epithelial characteristics. Importantly, EMT-CSC thereby required an $ALDH^+$ phenotype to switch to non-EMT-CSC and to develop metastasis successfully. More recently, a CD44-regulated signaling pathway mediated by phosphorylation of glycogen synthase kinase 3β (GSK3β) has been identified and has shown the potential to affect CSC phenotypes [21]. Inhibition of GSK3β could reduce the formation of CSCs-enriched tumor spheres and "holoclone" colonies. Reduction of the expression of stem cell markers and upregulation of the differentiation markers were also found in the $CD44^{high}ESA^{high}$ cell fraction by GSK3β inhibition. GSK3β knockdown could induce CSCs reversing from EMT and back to the epithelial CSC phenotype. In another study, Yang et al. identified a mechanism in which the EMT inducer Twist1 elicits cancer cell movement through activation of RAC1 [22]. They found that Twist1 cooperates with BMI1 to suppress let-7i expression, which results in up-regulation of NEDD9 and DOCK3, leading to RAC1 activation and enabling mesenchymal-mode movement in three-dimensional environments. Moreover, the suppression of let-7i contributes to Twist1-induced stem-like properties. These tumor cells expressing a stem-like cancer cell phenotype could transit from non-motile, epithelial-like cells to motile mesenchymal cells. Reversing EMT in prostate cancer

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