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Review

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OCT4's role and mechanism underlying oral squamous cell carcinoma

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Abstract: Oral squamous cell carcinoma (OSCC), a common malignancy of the head and neck, ranks sixth worldwide in terms of cancers with the most negative impact, owing to tumor relapse rates, cervical lymphnode metastasis, and the lack of an efficacious systemic therapy. Its prognosis is poor, and its mortality rate is high. Octamer-binding transcription factor 4 (OCT4) is a member of the Pit-Oct-Unc (POU) family and is a key reprogramming factor that produces a marked effect in preserving the pluripotency and self-renewal state of embryonic stem cells (ESCs). According to recent studies, OCT4 participates in retaining the survival of OSCC cancer stem cells (CSCs), which has far-reaching implications for the occurrence, recurrence, metastasis, and prognosis of oral carcinogenesis. Therefore, we summarize the structure, subtypes, and function of OCT4 as well as its role in the occurrence, progression, and prognosis of OSCC.

Key words: Cancer stem cell (CSC); Octamer-binding transcription factor 4 (OCT4); Oral squamous cell carcinoma (OSCC); Prognosis; Signaling pathway

1 Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy and accounts for more than 90% of oral cancers, with 300 000 new cases per year on average; thus, it has become a worldwide public health concern (Bray et al., 2018; Siegel et al., 2019; He et al., 2021; Pang et al., 2021). The main hazardous behaviors are smoking, drinking alcohol, and chewing betel quid (Huang et al., 2020). Treatment options include surgery, radiation, chemotherapy, or combined treatment, based on cancer location, tumor type, and stage (Tahmasebi et al., 2020). Despite considerable improvements in gauging and treatment protocols, five-year survival remained at approximately 50% in 2020, unchanged from the previous years (Moro et al., 2018; Zhang et al., 2019; Mishra et al., 2020). Low treatment response, high recurrence rate, and local metastasis are the major causes of therapeutic failure and bleak prognosis. Consequently, finding the molecular mechanism of OSCC occurrence and development and searching for specific tumor markers have already become urgent matters.

With advances in basic research on tumors, it has been discovered that tumor progression is associated with cancer stem cells (CSCs), which are a portion of tumor tissue with stem-cell nature and possessing the ability to proliferate infinitely, self-renew, as well as initiate and promote tumors (Cai et al., 2016; Olivares-Urbano et al., 2020; Oshimori, 2020). The CSC theory originated from leukemia (Griffin and Lowenberg, 1986), and multiple studies have demonstrated its prognostic role in solid organ malignancies such as glioblastoma (Lathia et al., 2015; Gimple et al., 2019; Sharifzad et al., 2019), non-small-cell lung cancer (Heng et al., 2019; Deng et al., 2020), breast cancer (Yang et al., 2017; Bai et al., 2018; Quaglino et al., 2020), hepatocellular carcinoma (Liu YC et al.,

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2020; Dai et al., 2021; Wong et al., 2021), esophageal squamous cell carcinoma (Wu et al., 2019), and oral cancer (Rodini et al., 2017; Liu YF et al., 2020; Ma et al., 2020; Al-Magsoosi et al., 2021; Feng et al., 2021). According to the theory, CSCs are a unique subset of cancer cells with high tumorigenicity and potential for metastasis. In addition, they largely determine the biological properties of cancer, contributing to fast growth, invasion, and metastasis (Reya et al., 2001; Baillie et al., 2017). CSCs are also resistant to most forms of chemoradiotherapy, which explains the failure and repetition of anticancer therapy in many cancer patients, including OSCC patients (Nichols et al., 1998; da Silva et al., 2012; Rodini et al., 2017; Mishra et al., 2020; Sun et al., 2020).

The self-renewal capacity of CSCs can be sustained through certain endogenous signaling pathways, for instance wingless/integrated (Wnt), Notch, Hedgehog, B-cell-specific Moloney murine leukemia virus integration site 1 (BMI1), phosphatase and tensin homolog (Pten), bone morphogenetic protein (Bmp), and transforming growth factor-β (TGF-β) (Shin and Kim, 2018); when these pathways are out of balance, tumorigenesis can occur. Activation of Notch and Hedgehog has been found in leukemia and other cancers (Unden et al., 1996; Diévart et al., 1999; Nam et al., 2002; Nickoloff et al., 2003; Benson et al., 2004; Karhadkar et al., 2004; Olsen et al., 2004), and hematopoietic stem cells (HSCs) can undergo self-renewal by Bmp and Notch signaling (Karanu et al., 2000; Varnum-Finney et al., 2000; Bhardwaj et al., 2001). In addition, elevated levels of β-catenin and Wnt proteins enhance protein stability, which is activated in colorectal, melanoma, breast, and oral cancers (Gat et al., 1998; Iwai et al., 2010; Liu et al., 2010; Fujii et al., 2011; Ravindran and Devaraj, 2012; Zhan et al., 2017).

To identify CSCs, one can use cell surface markers; familiar CSC biomarkers in OSCC include octamer-binding transcription factor 4 (OCT4), cluster of differentiation 44 (CD44), sex-determining region Y-box 2 (SOX2), Nanog homeobox (NANOG), and aldehyde dehydrogenase 1 (ALDH1) (Curtarelli et al., 2018; Gliagias et al., 2019). OCT4, as a considerable regulatory factor maintaining stem-cell pluripotency, is specifically expressed in embryonic stem cells (ESCs) and is inextricably associated with the relapse and drug resistance of various solid tumors in the human body. It may be a key gene for the potential regeneration and differentiation of OSCC. Therefore, this article reviews the function and possible mechanism of OCT4 in OSCC.

2 OCT4 overview

2.1 Structure of OCT4

2.1.1 Structure of the *OCT4* gene

OCT4 (encoded by POU class 5 homeobox 1 (*POU5f1*), also called *OCT3*, *OCT3/4*) belongs to subgroup V of the POU transcription-factor family (Chiou et al., 2008; Sawant et al., 2016; Khan et al., 2018), whose members regulate transcription of the target gene by specifically integrating with an octameric sequence motif AGTCAAAT, and hence are named *OCT4* (Bourguignon et al., 2012). *OCT4* is oriented on chromosomes 6p21.31 and 17B1 in the human and mouse genomes, respectively, with a length of 16.4 kb. Moreover, *OCT4* isoform 1 is one of the major isoforms of transcription, with five exons and four introns (Zhao et al., 2020).

2.1.2 Structure of the OCT4 protein

The relative molecular weight of the OCT4 protein is 18 kDa, and it is composed of three functional domains: the POU-binding domain, N-terminal transcriptional activation domain, and C-terminal cell-type-specific transactivation domain (Herr and Cleary, 1995; Pesce and Scholer, 2001). The POU-binding domain includes two subunits: the N-terminal and the C-terminal. An acidic and proline-rich conserved domain resides at the N-terminus of the POU family (POUs), while the C-terminus is a conventional homeodomain (POUh), which is full of proline, serine, and threonine residues; POUs and POUh are linked by connecting peptides.

2.2 Subtypes of the *OCT4* gene

OCT4 has three isoforms in human tissues: OCT-4A, OCT-4B, and OCT-4B1 (Wang et al., 2011; Kong et al., 2014). OCT-4A and OCT-4B consist of 360 and 265 amino acids, respectively, of which 225 amino acids at the C-terminus are the same, but different sequences are formed at the N-terminus. The N-terminus of OCT-4A can bind to DNA and activate transcription, while the N-terminus of OCT-4B inhibits binding to DNA and the activity of the OCT4 activator to activate its transcription. Therefore, the biological functions

of OCT-4A and OCT-4B are different. A transcription factor known as OCT-4A is located in the nucleus of ESCs, controlling a number of stem-cell genes, while OCT-4B is located in ESC cytoplasm and is insufficient to maintain an undifferentiated state and activate transcription of the *OCT4* gene (Cauffman et al., 2006; Lee et al., 2006; Chiou et al., 2008; Kotoula et al., 2008; Reers et al., 2014). OCT-4B1 is mainly expressed in pluripotent cells (Liu et al., 2017), and it shares the same amino terminal and partial POU-binding region with OCT-4B, while the rest of the amino-acid sequence is different. OCT-4B1 can enhance the anti-apoptotic functions of cells and regulate their pluripotent potential, which may be related to tumor progression.

2.3 Function of the *OCT4* gene

As a transcription factor, OCT4 exists in the inner cell mass of blastocysts and has a marked effect in retaining the pluripotency and self-renewal of ESCs, germ cells, and adult stem cells (Chiou et al., 2008; Sawant et al., 2016; Tegginamani et al., 2020; Han et al., 2022). The *OCT4* gene, a significant ESC marker, regulates the growth and development of the body in the early stage, but its expression is weakened after cell differentiation and maturation (Rizzino and Wuebben, 2016). In addition, OCT4, SOX2, and NANOG work together in regulating the cell reprogramming of CSCs and somatic cells (Naini et al., 2019). These key transcription factors can reprogram human somatic fibroblasts into ESC-like pluripotent cells, which are called induced pluripotent stem cells (iPSCs) (Ghazi et al., 2020; Cao et al., 2022; Shen et al., 2022; Ilia et al., 2023). In OSCC, OCT4 produces a marked increase in tumor transformation, tumorigenicity, invasion, and metastasis (Chang et al., 2008; Chiou et al., 2008; Kim and Nam, 2011; Huang et al., 2014). Some studies have also proposed that OCT4 may promote tumorigenesis by regulating epithelial-mesenchymal transition (EMT), so it is conjectured to be a potential marker of CSCs (Baillie et al., 2017).

3 Expression and prognostic assessment value of OCT4 in OSCC

Because of its complex structure and reprogramming function in CSCs and somatic cells, OCT, as a marker of ESCs, is also expressed in primordial germ cells and their tumors, as well as various somatic tumors. In addition, reactivation of OCT4 has been observed in many cancers, such as lung cancer (Li et al., 2019; Lu CS et al., 2020), esophageal cancer (Vijayakumar et al., 2020), gastric cancer (Chen et al., 2019; Basati et al., 2020), breast cancer (Lu HQ et al., 2020), and bladder cancer (Lu et al., 2017). It plays a role as a tumor biomarker and promoter, as well as a key role in the occurrence and development of multiple malignancies. Therefore, we probed the expression of OCT4 and its prognostic assessment value in OSCC.

3.1 Expression of OCT4 in OSCC and correlation with clinicopathological features

Numerous studies have revealed that OSCC expresses OCT4. Rodrigues et al. (2018) showed that in tongue squamous-cell carcinoma samples, only 3.33% (2/60) were devoid of OCT4 expression, 36.66% (22/60) were considered weakly positive, and 60.00% (36/60) were considered strongly positive. Vijayakumar et al. (2020) performed immunohistochemical staining on 20 cases of OSCC, 20 cases of oral epithelial dysplasia (OED), and 25 normal oral mucosa (NOM) samples. Although less expressed in OSCC (3.97%) or OED (8.66%), OCT4 was significantly different compared to NOM (0.00%). Studies by Baillie et al. (2017), Lee et al. (2019), and Mishra et al. (2020) have shown similar increases in OCT4 expression in oral cancers. Compared with OED, Rao et al. (2020) found OSCC to express significantly higher levels of OCT4, and negative and weak expression was found in 60% (24/40) and 40% (16/40) of OED cases, respectively; while in OSCC, there were 45% (18/44) weakly positive cases, 35% (14/44) strongly positive cases, and 20% (8/44) negative cases for OCT4. The expression of OCT4 in OSCC samples was not related to the clinicopathological parameters of age, sex, history of habits, or histology grade, but showed a relationship to tumor site, lymph-node metastasis, and tumor node metastasis (TNM) stage. Lymph-node metastatic cases with strongly positive staining accounted for 70% of all cases (14/20), whereas positive staining was absent in all nonmetastatic cases.

However, there have been contradictory conclusions. In the study by Fu et al. (2016), OCT4 expression was slightly, but not significantly, higher in patients

without lymph-node metastasis. Based on 45 OSCC samples and 15 OED samples, Ghazi et al. (2020) discovered that OCT4 expression differed significantly with age in OSCC tumor groups. Expression of OCT4 in young patients (<60 years old) was substantially higher than in elderly patients (>60 years old) (P=0.032). It was also significantly higher in OSCC grade III patients than in grade I or II cases, but the relationship was insignificantly different (P=0.84). Experiments by Chiou et al. (2008) showed a positive correlation between increased OCT4 expression and progression of oral cancers, as well as medium to poor differentiation, but not with lymph-node metastasis. In addition, more OCT4 nuclear staining was observed in grades III and IV oral cancer tissues than in grades I and II tissues. In summary, we can conclude that OCT4 is highly expressed in OSCC, but its relationship with patient age and lymph-node metastasis remains to be further explored.

3.2 Prognostic assessment value of OCT4 in OSCC

The prognostic significance of OCT4 has been noted in cervical carcinomas, renal-cell carcinomas, and breast cancer (Rasti et al., 2018; Tulake et al., 2018; Zhang et al., 2018). Kaplan-Meier analysis was used to evaluate the impact of OCT4 on survival of OSCC patients, and the results indicated that the overall survival rate for OCT4 immunohistochemical positive cases was significantly worse than that for negative ones (Chiou et al., 2008; Rao et al., 2020). Kaplan-Meier analysis by Chiou et al. (2008) and Singh et al. (2018) also predicted that the survival rate for patients with triple-positive OSCC (OCT4/NANOG/CD133) would be the worst. Fan et al. (2017) also confirmed that high expression of OCT4 and NANOG was related to lower overall survival (OS) in head and neck squamous-cell carcinoma (HNSCC) patients. Sawant et al. (2016) and Roy et al. (2019) found that an increase in OCT4 expression was relevant to poor prognosis and cisplatin resistance in OSCC. According to Pandian et al. (2022), gastric diffuse, poorly differentiated, and stage III tumors consistently express 84 genes that correlate positively with the activation pattern of the available *OCT4* gene sets. Therefore, positive expression of OCT4 has a significant effect on the chemotherapy response and survival rate of OSCC patients, shows independent prognostic value, and may provide a new observation metric for OSCC clinical treatment.

In summary, OCT4 is highly expressed in OSCC tissues, and its expression level is tightly related to lymph-node metastasis and pathological stage. When highly expressed, OCT4 can promote the occurrence and development of tumors, resulting in poor prognosis and a low survival rate.

4 Important regulatory signaling pathways related to OCT4 in OSCC

Relevant studies have found that the mechanism by which OCT4 maintains stem-cell self-renewal and multipotential differentiation may be regulated by Wnt, TGF-β, Hedgehog, and other signaling pathways (Pandian et al., 2022). In OSCC, we found activation of the Wnt/β-catenin, Lin28/hsa-Let-7 (Let-7), and nuclear factor of activated T-cells (NFAT) pathways (Chien et al., 2015; Nguyen et al., 2022; Yang et al., 2022). We will elaborate on these pathway mechanisms of OCT4 in OSCC below (Fig. 1).

4.1 Wnt/β-catenin signaling pathway

The Wnt signaling pathway is a complicated protein-interaction network that is closely linked to embryonic development, as well as tumor formation and development. It is well known that Wnt signaling is classically mediated by Wnt signaling transmission to glutathione (GSH) after entering the cell, and that activating GSH inhibits the activity of the compound (Axin/β-catenin/adenomatous polyposis coli (APC)/glycogen synthase kinase 3 (GSK3)/casein kinase-1 (CK1)) (Zhan et al., 2017). Because of this, β-catenin cannot be phosphorylated by GSK-3β; it accumulates in the cytoplasm, migrates to the nucleus, and combines with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors to regulate gene expression by activating TCF transcriptional activity. The Wnt pathways are normally closed, but when they are activated, abnormal cell proliferation and differentiation occur, eventually leading to the formation of tumors. Observations were made by Ravindran and Devaraj (2012) regarding Wnt/β-catenin reactivation in oral cancers. Ravindran et al. (2015) revealed that the expression patterns of β-catenin and OCT4 have a significant positive correlation in oral carcinoma, based on Spearman correlation analysis. Wang et al. (2021) found that Wnt/β-catenin signaling was abnormally activated in OSCC SCC-55 cells, while *OCT4* gene

transcription in SCC-55 cells was significantly downregulated when β-catenin was silenced, resulting in reduced efficiency of tumor cell proliferation, invasion, and colony formation.

4.2 Lin28/Let-7 signaling pathway

Lin28 is a structurally highly conserved RNA-binding protein in advanced eukaryotes, exerting a major role in normal development of the human body and in some disease states. Let-7 microRNAs (miRNAs) are known to target many important oncogenes as tumor suppressors in head and neck cancers (HNCs) (Thomaidou et al., 2022). In human cells, Lin28 negatively regulates transcription of Let-7, inhibits synthesis of Let-7 in mature cells, upregulates the cell cycle, and promotes stem-cell proliferation. In human tumor stem cells, Lin28 can selectively inhibit the processing and synthesis of mature Let-7 cells, thereby promoting tumor stem-cell proliferation and inhibiting apoptosis, which ultimately leads to tumorigenesis. In human tumor cells, Lin28 is highly expressed, while Let-7 is expressed at low levels. It is generally believed that Lin28 and Let-7 are a pair of mutually inhibiting and negatively regulating factors, so they are known as the double-negative feedback loop or regulatory loop. When Lin28 is normally expressed, it can combine with OCT4, SOX2, and NANOG to reprogram human fibroblast cells into multifunctional stem cells, but its overexpression can cause malignant transformation of cells, which has been confirmed by researchers in hepatocellular carcinoma, lung cancer, and other tumors. Chien et al. (2015) also demonstrated that the Lin28B/Let-7 pathway, as a driving mechanism, promotes ESC stemness properties by positively regulating OCT4 and SOX2 expression and inducing reprogramming in OSCC cells.

4.3 NFAT signaling pathway

NFAT family is a group of transcription factors that are dependent on calcium/calcineurin. Hyperphosphorylation of NFAT is confined to the cytoplasm during the resting state. When the Ca^{2+} channel on the cell membrane is opened and the intracellular Ca^{2+} concentration remains at a high level, a conformational change in NFAT occurs, and dephosphorylation exposes the nuclear localization sequence. Subsequently, it binds to the target promoter element and regulates transcription of specific response genes which regulate a wide variety of life activities of cells. Studies have shown that regulation of NFAT is not limited to neurodevelopment or the immune system, but also plays a significant role in various tumor-cell activities and malignant transformation. For example, NFATc3 plays a pivotal role in the pathophysiological process of diseases with a high degree of malignancy, including esophageal cancer, triple-negative breast cancer, and glioblastoma. Lee et al. (2019) found that NFATc3 also exerts its action in OSCC. NFATc3 is located upstream of OCT4, and regulates CSC characteristics such as migration and chemical resistance through upregulation of OCT4, showing that the NFATc3–OCT4 axis may become a necessary therapeutic target for OSCC.

In summary, Wnt/β-catenin signaling is currently a hotspot for research. Yuan et al. (2010) found that OCT4 plays an important role in hepatocellular carcinoma through the TGF-β signaling pathway. Another group (Wen et al., 2013) found that OCT4's involvement in keeping drug-resistant colon cancer cells alive may be related to the signal-transducer and activator of the transcription-3 (STAT3)/survivin signaling pathway. Pandian et al. (2022) found that OCT4 is positively associated with dysregulation of the TGF-β, glioma-associated oncogene homolog (GLI), polycomb repressive complex 2/enhancer of zeste homolog 2 (PRC2/EZH2), Wnt, Kirsten rat sarcoma viral oncogene homolog (KRAS), serine/threonine-kinase 33 (STK33), and Yes-associated protein (YAP) signaling pathways in diffuse subtype gastric cancer. OCT4, however, has yet to be explored in relation to the occurrence, development, and prognosis of OSCC via these pathways.

5 Current situation and prospects

Surgical resection combined with neck dissection is the most common treatment regimen for oral cancer, followed by radiotherapy and chemotherapy. However, as a result of tumor recurrence and drug resistance, the prognosis is still not optimistic (Swain et al., 2020). The existence of heterogeneous subsets of CSCs is considered one of the leading causes for the failure of OSCC treatment (Gupta et al., 2021). CSCs are resistant to chemoradiotherapy drugs such as cisplatin (Okamoto et al., 2009; Noto et al., 2013; Nör et al., 2014; Tsai et al., 2014), paclitaxel (Okamoto et al., 2009; Zhang et al., 2010), and etoposide (Song et al.,

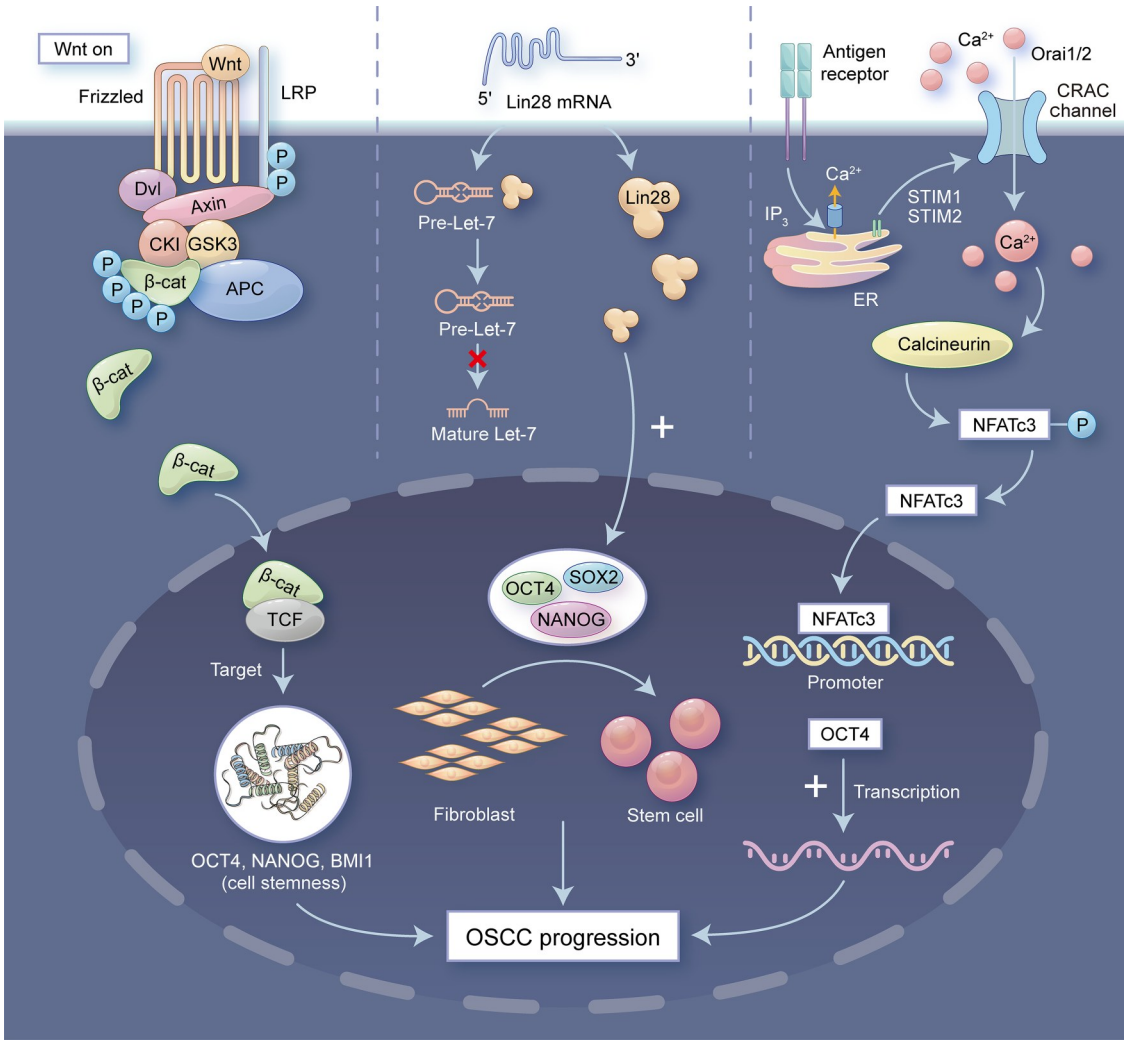

Fig. 1 Three important pathway mechanisms of OCT4 in OSCC. OCT4: octamer-binding transcription factor 4; OSCC: oral squamous cell carcinoma; Wnt: wingless/integrated; LRP: leucine-responsive regulatory protein; Dvl: dishevelled; CK1: casein kinase-1; GSK3: glycogen synthase kinase 3; β-cat: β-catenin; APC: adenomatous polyposis coli; TCF: T-cell factor; NANOG: Nanog homeobox; BMI1: B-cell-specific Moloney murine leukemia virus integration site 1; mRNA: messenger RNA; SOX2: sex-determining region Y-box 2; CRAC: Ca^{2+} release-activated Ca^{2+}; IP_3: inositol 1, 4, 5-trisphosphate; ER: endoplasmic reticulum; STIM: stromal interaction molecule; NFATc3: nuclear factor of activated T-cells c3; P: phosphorylated.

2010). Accordingly, oral cancer treatment targeting tumor stem cells may prove to be an important new approach (Satpute et al., 2013).

As a core transcription factor that enables ESCs to maintain self-renewal and differentiation potential, OCT4 shows high expression in OSCC and plays a considerable role in maintaining tumorigenicity, invasiveness, and drug resistance. In addition, it regulates and acts together with multiple factors and multiple signaling pathways, which offers a new direction for further investigation of oral CSCs. These cells may become a research hotspot of molecular targeted therapy for oral cancer in coming years. *OCT4* gene knockdown can reduce the self-renewal ability and stem-cell transformation of HNSCC (Nathansen et al., 2021), inhibit the proliferation, migration, and invasion of cancer cells, and exert antitumor effects (Xie et al., 2022). Specific targeted molecules such as transient-receptor-potential melastatin-subfamily member 7 (TRPM7) (Chen et al., 2022) and 3-photonoinoside-dependent kinase 1 (PDK1) (Pai et al., 2021) can inhibit the metastasis and chemo/radioresistant resistance of cancer cells by downregulating the expression of OTC4 and regulating multiple signaling pathways;

this may provide effective treatment ideas and strategies to enhance antitumor efficacy. However, most current oral cancer research is based on cell experiments, and cell research involves many factors such as personal operation and laboratory conditions, as well as the existence of pseudogene transcription, DNA contamination, and *OCT4* subtypes. The false-positive rate of OCT4 was obviously increased, which makes determining the nature of the tumor complicated. Therefore, the clinical use of OCT4 as an indicator of OSCC cannot be the sole basis for diagnosis or treatment planning. Further studies on the isolation and identification of *OCT4* subtypes are needed, as well as clinical trials.

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Author contributions

Yuwei DAI contributed to the conception of the study; Ziqiong WU and Yitong CHEN contributed significantly to analysis and manuscript preparation; Xinjian YE performed the data analysis and wrote the manuscript; Chaowei WANG provided ideas and financial support for the review; Huiyong ZHU helped perform the analysis with constructive discussions and provided substantive guidance on the paper's ideas and the entire writing process. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Yuwei DAI, Ziqiong WU, Yitong CHEN, Xinjian YE, Chaowei WANG, and Huiyong ZHU declare that they have no conflict of interest.

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

References

Al-Magsoosi MJN, Lambert DW, Ali Khurram S, et al., 2021. Oral cancer stem cells drive tumourigenesis through activation of stromal fibroblasts. *Oral Dis*, 27(6):1383-1393. https://doi.org/10.1111/odi.13513

Bai XP, Ni J, Beretov J, et al., 2018. Cancer stem cell in breast cancer therapeutic resistance. *Cancer Treat Rev*, 69:152-163. https://doi.org/10.1016/j.ctrv.2018.07.004

Baillie R, Tan ST, Itinteang T, 2017. Cancer stem cells in oral cavity squamous cell carcinoma: a review. *Front Oncol*, 7:112. https://doi.org/10.3389/fonc.2017.00112

Basati G, Mohammadpour H, Emami Razavi A, 2020. Association of high expression levels of SOX2, NANOG, and OCT4 in gastric cancer tumor tissues with progression and poor prognosis. *J Gastrointest Cancer*, 51(1):41-47. https://doi.org/10.1007/s12029-018-00200-x

Benson RA, Lowrey JA, Lamb JR, et al., 2004. The Notch and Sonic hedgehog signalling pathways in immunity. *Mol Immunol*, 41(6-7):715-725. https://doi.org/10.1016/j.molimm.2004.04.017

Bhardwaj G, Murdoch B, Wu D, et al., 2001. Sonic hedgehog induces the proliferation of primitive human hematopoietic cells *via* BMP regulation. *Nat Immunol*, 2(2):172-180. https://doi.org/10.1038/84282

Bourguignon LYW, Wong G, Earle C, et al., 2012. Hyaluronan-CD44v3 interaction with Oct4-Sox2-Nanog promotes miR-302 expression leading to self-renewal, clonal formation, and cisplatin resistance in cancer stem cells from head and neck squamous cell carcinoma. *J Biol Chem*, 287(39): 32800-32824. https://doi.org/10.1074/jbc.M111.308528

Bray F, Ferlay J, Soerjomataram I, et al., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 68(6):394-424. https://doi.org/10.3322/caac.21492

Cai JH, He BX, Li XM, et al., 2016. Regulation of tumorigenesis in oral epithelial cells by defined reprogramming factors Oct4 and Sox2. *Oncol Rep*, 36(2):651-658. https://doi.org/10.3892/or.2016.4851

Cao YW, Tian WT, Cao L, et al., 2022. Generation of an induced pluripotent stem cell JTUi005-A from a patient with neuronal intranuclear inclusion disease. *Stem Cell Res*, 65: 102938. https://doi.org/10.1016/j.scr.2022.102938

Cauffman G, Liebaers I, van Steirteghem A, et al., 2006. POU5F1 isoforms show different expression patterns in human embryonic stem cells and preimplantation embryos. *Stem Cells*, 24(12):2685-2691. https://doi.org/10.1634/stemcells.2005-0611

Chang CC, Shieh GS, Wu P, et al., 2008. Oct-3/4 expression reflects tumor progression and regulates motility of bladder cancer cells. *Cancer Res*, 68(15):6281-6291. https://doi.org/10.1158/0008-5472.CAN-08-0094

Chen BR, Zhu ZP, Li LL, et al., 2019. Effect of overexpression of Oct4 and Sox2 genes on the biological and oncological characteristics of gastric cancer cells. *Onco Targets Ther*, 12:4667-4682. https://doi.org/10.2147/OTT.S209734

Chen TM, Huang CM, Hsieh MS, et al., 2022. TRPM7 via calcineurin/NFAT pathway mediates metastasis and chemotherapeutic resistance in head and neck squamous cell carcinoma. *Aging*, 14(12):5250-5270. https://doi.org/10.18632/aging.204154

Chien CS, Wang ML, Chu PY, et al., 2015. Lin28B/Let-7 regulates expression of Oct4 and Sox2 and reprograms oral squamous cell carcinoma cells to a stem-like state. *Cancer Res*, 75(12):2553-2565. https://doi.org/10.1158/0008-5472.CAN-14-2215

Chiou SH, Yu CC, Huang CY, et al., 2008. Positive correlations of Oct-4 and Nanog in oral cancer stem-like cells and high-grade oral squamous cell carcinoma. *Clin Cancer Res*, 14(13):4085-4095. https://doi.org/10.1158/1078-0432.CCR-07-4404

Curtarelli RB, Gonçalves JM, dos Santos LGP, et al., 2018. Expression of cancer stem cell biomarkers in human head and neck carcinomas: a systematic review. *Stem Cell Rev Rep*, 14(6):769-784. https://doi.org/10.1007/s12015-018-9839-4

da Silva SD, Hier M, Mlynarek A, et al., 2012. Recurrent oral cancer: current and emerging therapeutic approaches. *Front Pharmacol*, 3:149. https://doi.org/10.3389/fphar.2012.00149

Dai XM, Guo YX, Hu Y, et al., 2021. Immunotherapy for targeting cancer stem cells in hepatocellular carcinoma. *Theranostics*, 11(7):3489-3501. https://doi.org/10.7150/thno.54648

Deng KY, Liu L, Tan XM, et al., 2020. Wip1 promotes cancer stem cell properties by inhibiting p38 MAPK in NSCLC. *Signal Transduct Target Ther*, 5:36. https://doi.org/10.1038/s41392-020-0126-x

Diévart A, Beaulieu N, Jolicoeur P, 1999. Involvement of *Notch1* in the development of mouse mammary tumors. *Oncogene*, 18(44):5973-5981. https://doi.org/10.1038/sj.onc.1202991

Fan ZN, Li MX, Chen XB, et al., 2017. Prognostic value of cancer stem cell markers in head and neck squamous cell carcinoma: a meta-analysis. *Sci Rep*, 7:43008. https://doi.org/10.1038/srep43008

Feng J, Li YX, Wen N, 2021. Characterization of cancer stem cell characteristics and development of a prognostic stemness index cell-related signature in oral squamous cell carcinoma. *Dis Markers*, 2021:1571421. https://doi.org/10.1155/2021/1571421

Fu TY, Hsieh IC, Cheng JT, et al., 2016. Association of OCT4, SOX2, and NANOG expression with oral squamous cell carcinoma progression. *J Oral Pathol Med*, 45(2):89-95. https://doi.org/10.1111/jop.12335

Fujii M, Katase N, Lefeuvre M, et al., 2011. Dickkopf (Dkk)-3 and β-catenin expressions increased in the transition from normal oral mucosal to oral squamous cell carcinoma. *J Mol Histol*, 42(6):499-504. https://doi.org/10.1007/s10735-011-9357-z

Gat U, Dasgupta R, Degenstein L, et al., 1998. De novo hair follicle morphogenesis and hair tumors in mice expressing a truncated β-catenin in skin. *Cell*, 95(5):605-614. https://doi.org/10.1016/s0092-8674(00)81631-1

Ghazi N, Aali N, Shahrokhi VR, et al., 2020. Relative expression of SOX2 and OCT4 in oral squamous cell carcinoma and oral epithelial dysplasia. *Rep Biochem Mol Biol*, 9(2):171-179. https://doi.org/10.29252/rbmb.9.2.171

Gimple RC, Bhargava S, Dixit D, et al., 2019. Glioblastoma stem cells: lessons from the tumor hierarchy in a lethal cancer. *Genes Dev*, 33(11-12):591-609. https://doi.org/10.1101/gad.324301.119

Gliagias V, Wotman M, Herman SW, et al., 2019. Investigating the role of octamer binding transcription factor-4 (Oct-4) in oral cavity squamous cell carcinoma: a systematic review and meta-analysis. *Am J Otolaryngol*, 40(2):282-288. https://doi.org/10.1016/j.amjoto.2018.12.011

Griffin JD, Lowenberg B, 1986. Clonogenic cells in acute myeloblastic leukemia. *Blood*, 68(6):1185-1195. https://doi.org/10.1182/blood.V68.6.1185.1185

Gupta S, Kumar P, Das BC, 2021. HPV$^{+ve/-ve}$ oral-tongue cancer stem cells: a potential target for relapse-free therapy. *Transl Oncol*, 14(1):100919. https://doi.org/10.1016/j.tranon.2020.100919

Han D, Wu GM, Chen R, et al., 2022. A balanced Oct4 interactome is crucial for maintaining pluripotency. *Sci Adv*, 8(7):eabe4375. https://doi.org/10.1126/sciadv.abe4375

He SQ, Zhang W, Li X, et al., 2021. Oral squamous cell carcinoma (OSCC)-derived exosomal MiR-221 targets and regulates phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) to promote human umbilical vein endothelial cells migration and tube formation. *Bioengineered*, 12(1):2164-2174. https://doi.org/10.1080/21655979.2021.1932222

Heng WS, Gosens R, Kruyt FAE, 2019. Lung cancer stem cells: origin, features, maintenance mechanisms and therapeutic targeting. *Biochem Pharmacol*, 160:121-133. https://doi.org/10.1016/j.bcp.2018.12.010

Herr W, Cleary MA, 1995. The POU domain: versatility in transcriptional regulation by a flexible two-in-one DNA-binding domain. *Genes Dev*, 9(14):1679-1693. https://doi.org/10.1101/gad.9.14.1679

Huang CF, Xu XR, Wu TF, et al., 2014. Correlation of ALDH1, CD44, OCT4 and SOX2 in tongue squamous cell carcinoma and their association with disease progression and prognosis. *J Oral Pathol Med*, 43(7):492-498. https://doi.org/10.1111/jop.12159

Huang GZ, Wu QQ, Zheng ZN, et al., 2020. M6A-related bioinformatics analysis reveals that HNRNPC facilitates progression of OSCC via EMT. *Aging*, 12(12):11667-11684. https://doi.org/10.18632/aging.103333

Ilia K, Shakiba N, Bingham T, et al., 2023. Synthetic genetic circuits to uncover and enforce the OCT4 trajectories of successful reprogramming of human fibroblasts. bioRxiv, preprint. https://doi.org/10.1101/2023.01.25.525529

Iwai S, Yonekawa A, Harada C, et al., 2010. Involvement of the Wnt-β-catenin pathway in invasion and migration of oral squamous carcinoma cells. *Int J Oncol*, 37(5):1095-1103. https://doi.org/10.3892/ijo_00000761

Karanu FN, Murdoch B, Gallacher L, et al., 2000. The Notch ligand Jagged-1 represents a novel growth factor of human hematopoietic stem cells. *J Exp Med*, 192(9):1365-1372. https://doi.org/10.1084/jem.192.9.1365

Karhadkar SS, Bova GS, Abdallah N, et al., 2004. Hedgehog signalling in prostate regeneration, neoplasia and metastasis. *Nature*, 431(7009):707-712. https://doi.org/10.1038/nature02962

Khan W, Augustine D, Rao RS, et al., 2018. Stem cell markers SOX-2 and OCT-4 enable to resolve the diagnostic dilemma

between ameloblastic carcinoma and aggressive solid multicystic ameloblastoma. *Adv Biomed Res*, 7:149. https://doi.org/10.4103/abr.abr_135_18

Kim RJ, Nam JS, 2011. OCT4 expression enhances features of cancer stem cells in a mouse model of breast cancer. *Lab Anim Res*, 27(2):147-152. https://doi.org/10.5625/lar.2011.27.2.147

Kong QY, Liu L, Huang YJ, et al., 2014. The effect of octamer-binding transcription factor 4B1 on microRNA signals in human dental pulp cells with inflammatory response. *J Endod*, 40(1):101-108. https://doi.org/10.1016/j.joen.2013.09.030

Kotoula V, Papamichos SI, Lambropoulos AF, 2008. Revisiting OCT4 expression in peripheral blood mononuclear cells. *Stem Cells*, 26(1):290-291. https://doi.org/10.1634/stemcells.2007-0726

Lathia JD, Mack SC, Mulkearns-Hubert EE, et al., 2015. Cancer stem cells in glioblastoma. *Genes Dev*, 29(12):1203-1217. https://doi.org/10.1101/gad.261982.115

Lee J, Kim HK, Rho JY, et al., 2006. The human OCT-4 isoforms differ in their ability to confer self-renewal. *J Biol Chem*, 281(44):33554-33565. https://doi.org/10.1074/jbc.M603937200

Lee SH, Kieu C, Martin CE, et al., 2019. NFATc3 plays an oncogenic role in oral/oropharyngeal squamous cell carcinomas by promoting cancer stemness via expression of OCT4. *Oncotarget*, 10(23):2306-2319. https://doi.org/10.18632/oncotarget.26774

Li H, Wang LW, Shi SP, et al., 2019. The prognostic and clinicopathologic characteristics of OCT4 and lung cancer: a meta-analysis. *Curr Mol Med*, 19(1):54-75. https://doi.org/10.2174/1566524019666190308163315

Liu L, Huang R, Yang RQ, et al., 2017. OCT4B1 regulates the cellular stress response of human dental pulp cells with inflammation. *Biomed Res Int*, 2017:2756891. https://doi.org/10.1155/2017/2756891

Liu LK, Jiang XY, Zhou XX, et al., 2010. Upregulation of vimentin and aberrant expression of E-cadherin/β-catenin complex in oral squamous cell carcinomas: correlation with the clinicopathological features and patient outcome. *Mod Pathol*, 23(2):213-224. https://doi.org/10.1038/modpathol.2009.160

Liu YC, Yeh CT, Lin KH, 2020. Cancer stem cell functions in hepatocellular carcinoma and comprehensive therapeutic strategies. *Cells*, 9(6):1331. https://doi.org/10.3390/cells9061331

Liu YF, Yang M, Luo JJ, et al., 2020. Radiotherapy targeting cancer stem cells "awakens" them to induce tumour relapse and metastasis in oral cancer. *Int J Oral Sci*, 12:19. https://doi.org/10.1038/s41368-020-00087-0

Lu CS, Shieh GS, Wang CT, et al., 2017. Chemotherapeutics-induced Oct4 expression contributes to drug resistance and tumor recurrence in bladder cancer. *Oncotarget*, 8(19):30844-30858. https://doi.org/10.18632/oncotarget.9602

Lu CS, Shiau AL, Su BH, et al., 2020. Oct4 promotes M2 macrophage polarization through upregulation of macrophage colony-stimulating factor in lung cancer. *J Hematol Oncol*, 13:62. https://doi.org/10.1186/s13045-020-00887-1

Lu HQ, Xie YYR, Tran L, et al., 2020. Chemotherapy-induced S100A10 recruits KDM6A to facilitate OCT4-mediated breast cancer stemness. *J Clin Invest*, 130(9):4607-4623. https://doi.org/10.1172/JCI138577

Ma Z, Zhang C, Liu XT, et al., 2020. Characterisation of a subpopulation of $CD133^+$ cancer stem cells from Chinese patients with oral squamous cell carcinoma. *Sci Rep*, 10:8875. https://doi.org/10.1038/s41598-020-64947-9

Mishra S, Tiwari V, Arora A, et al., 2020. Increased expression of Oct4, Nanog and CD24 predicts poor response to chemo-radiotherapy and unfavourable prognosis in locally advanced oral squamous cell carcinoma. *Asian Pac J Cancer Prev*, 21(9):2539-2547. https://doi.org/10.31557/APJCP.2020.21.9.2539

Moro JDS, Maroneze MC, Ardenghi TM, et al., 2018. Oral and oropharyngeal cancer: epidemiology and survival analysis. *Einstein (Sao Paulo)*, 16(2):eAO4248. https://doi.org/10.1590/S1679-45082018AO4248

Naini FB, Aminishakib P, Abdollahi A, et al., 2019. Relative expression of OCT4, SOX2 and NANOG in oral squamous cell carcinoma versus adjacent non-tumor tissue. *Asian Pac J Cancer Prev*, 20(6):1649-1654. https://doi.org/10.31557/APJCP.2019.20.6.1649

Nam Y, Aster JC, Blacklow SC, 2002. Notch signaling as a therapeutic target. *Curr Opin Chem Biol*, 6(4):501-509. https://doi.org/10.1016/s1367-5931(02)00346-0

Nathansen J, Lukiyanchuk V, Hein L, et al., 2021. Oct4 confers stemness and radioresistance to head and neck squamous cell carcinoma by regulating the homologous recombination factors PSMC3IP and RAD54L. *Oncogene*, 40(24):4214-4228. https://doi.org/10.1038/s41388-021-01842-1

Nguyen A, Kim AH, Kang MK, et al., 2022. Chronic alcohol exposure promotes cancer stemness and glycolysis in oral/oropharyngeal squamous cell carcinoma cell lines by activating NFAT signaling. *Int J Mol Sci*, 23(17):9779. https://doi.org/10.3390/ijms23179779

Nichols J, Zevnik B, Anastassiadis K, et al., 1998. Formation of pluripotent stem cells in the mammalian embryo depends on the POU transcription factor Oct4. *Cell*, 95(3):379-391. https://doi.org/10.1016/s0092-8674(00)81769-9

Nickoloff BJ, Osborne BA, Miele L, 2003. Notch signaling as a therapeutic target in cancer: a new approach to the development of cell fate modifying agents. *Oncogene*, 22(42):6598-6608. https://doi.org/10.1038/sj.onc.1206758

Nör C, Zhang ZC, Warner KA, et al., 2014. Cisplatin induces Bmi-1 and enhances the stem cell fraction in head and neck cancer. *Neoplasia*, 16(2):137-146, W8. https://doi.org/10.1593/neo.131744

Noto Z, Yoshida T, Okabe M, et al., 2013. CD44 and SSEA-4 positive cells in an oral cancer cell line HSC-4 possess cancer stem-like cell characteristics. *Oral Oncol*, 49(8):787-795. https://doi.org/10.1016/j.oraloncology.2013.04.012

Okamoto A, Chikamatsu K, Sakakura K, et al., 2009. Expansion and characterization of cancer stem-like cells in squamous cell carcinoma of the head and neck. *Oral Oncol*, 45(7):633-639. https://doi.org/10.1016/j.oraloncology.2008.10.003

Olivares-Urbano MA, Griñán-Lisón C, Marchal JA, et al., 2020. CSC radioresistance: a therapeutic challenge to improve radiotherapy effectiveness in cancer. *Cells*, 9(7): 1651. https://doi.org/10.3390/cells9071651

Olsen CL, Hsu PP, Glienke J, et al., 2004. Hedgehog-interacting protein is highly expressed in endothelial cells but down-regulated during angiogenesis and in several human tumors. *BMC Cancer*, 4:43. https://doi.org/10.1186/1471-2407-4-43

Oshimori N, 2020. Cancer stem cells and their niche in the progression of squamous cell carcinoma. *Cancer Sci*, 111(11):3985-3992. https://doi.org/10.1111/cas.14639

Pai S, Yadav VK, Kuo KT, et al., 2021. PDK1 inhibitor BX795 improves cisplatin and radio-efficacy in oral squamous cell carcinoma by downregulating the PDK1/CD47/Akt-mediated glycolysis signaling pathway. *Int J Mol Sci*, 22(21):11492. https://doi.org/10.3390/ijms222111492

Pandian J, Panneerpandian P, Sekar BT, et al., 2022. OCT4-mediated transcription confers oncogenic advantage for a subset of gastric tumors with poor clinical outcome. *Funct Integr Genomics*, 22(6):1345-1360. https://doi.org/10.1007/s10142-022-00894-0

Pang X, Wang SS, Zhang M, et al., 2021. OSCC cell-secreted exosomal *CMTM6* induced M2-like macrophages polarization via ERK1/2 signaling pathway. *Cancer Immunol Immunother*, 70(4):1015-1029. https://doi.org/10.1007/s00262-020-02741-2

Pesce M, Scholer HR, 2001. *Oct-4*: gatekeeper in the beginnings of mammalian development. *Stem Cells*, 19(4):271-278. https://doi.org/10.1634/stemcells.19-4-271

Quaglino E, Conti L, Cavallo F, 2020. Breast cancer stem cell antigens as targets for immunotherapy. *Semin Immunol*, 47:101386. https://doi.org/10.1016/j.smim.2020.101386

Rao RS, Raju KL, Augustine D, et al., 2020. Prognostic significance of ALDH1, Bmi1, and OCT4 expression in oral epithelial dysplasia and oral squamous cell carcinoma. *Cancer Control*, 27(1):1073274820904959. https://doi.org/10.1177/1073274820904959

Rasti A, Mehrazma M, Madjd Z, et al., 2018. Co-expression of cancer stem cell markers OCT4 and NANOG predicts poor prognosis in renal cell carcinomas. *Sci Rep*, 8:11739. https://doi.org/10.1038/s41598-018-30168-4

Ravindran G, Devaraj H, 2012. Aberrant expression of β-catenin and its association with ΔNp63, Notch-1, and clinicopathological factors in oral squamous cell carcinoma. *Clin Oral Investig*, 16(4):1275-1288. https://doi.org/10.1007/s00784-011-0605-0

Ravindran G, Sawant SS, Hague A, et al., 2015. Association of differential β-catenin expression with Oct-4 and nanog in oral squamous cell carcinoma and their correlation with clinicopathological factors and prognosis. *Head Neck*, 37(7):982-993. https://doi.org/10.1002/hed.23699

Reers S, Pfannerstill AC, Maushagen R, et al., 2014. Stem cell profiling in head and neck cancer reveals an Oct-4 expressing subpopulation with properties of chemoresistance. *Oral Oncol*, 50(3):155-162. https://doi.org/10.1016/j.oraloncology.2013.12.006

Reya T, Morrison SJ, Clarke MF, et al., 2001. Stem cells, cancer, and cancer stem cells. *Nature*, 414(6859):105-111. https://doi.org/10.1038/35102167

Rizzino A, Wuebben EL, 2016. Sox2/Oct4: a delicately balanced partnership in pluripotent stem cells and embryogenesis. *Biochim Biophys Acta*, 1859(6):780-791. https://doi.org/10.1016/j.bbagrm.2016.03.006

Rodini CO, Lopes NM, Lara VS, et al., 2017. Oral cancer stem cells – properties and consequences. *J Appl Oral Sci*, 25(6): 708-715. https://doi.org/10.1590/1678-7757-2016-0665

Rodrigues MFSD, de Aquino Xavier FC, Andrade NP, et al., 2018. Prognostic implications of CD44, NANOG, OCT4, and BMI1 expression in tongue squamous cell carcinoma. *Head Neck*, 40(8):1759-1773. https://doi.org/10.1002/hed.25158

Roy S, Kar M, Roy S, et al., 2019. KLF4 expression in the surgical cut margin is associated with disease relapse of oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol*, 128(2):154-165. https://doi.org/10.1016/j.oooo.2019.02.021

Satpute PS, Hazarey V, Ahmed R, et al., 2013. Cancer stem cells in head and neck squamous cell carcinoma: a review. *Asian Pac J Cancer Prev*, 14(10):5579-5587. https://doi.org/10.7314/apjcp.2013.14.10.5579

Sawant S, Gokulan R, Dongre H, et al., 2016. Prognostic role of Oct4, CD44 and c-Myc in radio-chemo-resistant oral cancer patients and their tumourigenic potential in immunodeficient mice. *Clin Oral Invest*, 20(1):43-56. https://doi.org/10.1007/s00784-015-1476-6

Sharifzad F, Ghavami S, Verdi J, et al., 2019. Glioblastoma cancer stem cell biology: potential theranostic targets. *Drug Resist Updat*, 42:35-45. https://doi.org/10.1016/j.drup.2018.03.003

Shen HF, Li YL, Huang SH, et al., 2022. A real-time pluripotency reporter for the long-term and real-time monitoring of pluripotency changes in induced pluripotent stem cells. *Aging*, 14(10):4445-4458. https://doi.org/10.18632/aging.204083

Shin KH, Kim RH, 2018. An updated review of oral cancer stem cells and their stemness regulation. *Crit Rev Oncog*, 23(3-4):189-200. https://doi.org/10.1615/CritRevOncog.2018027501

Siegel RL, Miller KD, Jemal A, 2019. Cancer statistics, 2019. *CA Cancer J Clin*, 69(1):7-34. https://doi.org/10.3322/caac.21551

Singh A, Srivastava AN, Akhtar S, et al., 2018. Correlation of CD133 and Oct-4 expression with clinicopathological and demographic parameters in oral squamous cell carcinoma patients. *Natl J Maxillofac Surg*, 9(1):8-13. https://doi.org/10.4103/njms.NJMS_60_17

Song J, Chang I, Chen Z, et al., 2010. Characterization of side populations in HNSCC: highly invasive, chemoresistant and abnormal Wnt signaling. *PLoS ONE*, 5(7):e11456. https://doi.org/10.1371/journal.pone.0011456

Sun L, Xu YR, Zhang XM, et al., 2020. Mesenchymal stem cells functionalized sonodynamic treatment for improving therapeutic efficacy and compliance of orthotopic oral cancer. *Adv Mater*, 32(48):e2005295. https://doi.org/10.1002/adma.202005295

Swain N, Thakur M, Pathak J, et al., 2020. SOX2, OCT4 and NANOG: the core embryonic stem cell pluripotency regulators in oral carcinogenesis. *J Oral Maxillofac Pathol*, 24(2):368-373. https://doi.org/10.4103/jomfp.JOMFP_22_20

Tahmasebi E, Alikhani M, Yazdanian A, et al., 2020. The current markers of cancer stem cell in oral cancers. *Life Sci*, 249:117483. https://doi.org/10.1016/j.lfs.2020.117483

Tegginamani AS, Shivakumar VH, Kallarakkal TG, et al., 2020. Analysis of octamer-binding transcription factor-4 expression in oral leukoplakia. *J Oral Maxillofac Pathol*, 24(2):400. https://doi.org/10.4103/jomfp.JOMFP_272_19

Thomaidou AC, Batsaki P, Adamaki M, et al., 2022. Promising biomarkers in head and neck cancer: the most clinically important miRNAs. *Int J Mol Sci*, 23(15):8257. https://doi.org/10.3390/ijms23158257

Tsai LL, Hu FW, Lee SS, et al., 2014. Oct4 mediates tumor initiating properties in oral squamous cell carcinomas through the regulation of epithelial-mesenchymal transition. *PLoS ONE*, 9(1):e87207. https://doi.org/10.1371/journal.pone.0087207

Tulake W, Yuemaier R, Sheng L, et al., 2018. Upregulation of stem cell markers ALDH1A1 and OCT4 as potential biomarkers for the early detection of cervical carcinoma. *Oncol Lett*, 16(5):5525-5534. https://doi.org/10.3892/ol.2018.9381

Unden AB, Holmberg E, Lundh-Rozell B, et al., 1996. Mutations in the human homologue of *Drosophila patched* (*PTCH*) in basal cell carcinomas and the gorlin syndrome: different *in vivo* mechanisms of *PTCH* inactivation. *Cancer Res*, 56(20):4562-4565.

Varnum-Finney B, Xu LW, Brashem-Stein C, et al., 2000. Pluripotent, cytokine-dependent, hematopoietic stem cells are immortalized by constitutive Notch1 signaling. *Nat Med*, 6(11):1278-1281. https://doi.org/10.1038/81390

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

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

Wang YJ, Meng L, Hu HY, et al., 2011. Oct-4B isoform is differentially expressed in breast cancer cells: hypermethylation of regulatory elements of Oct-4A suggests an alternative promoter and transcriptional start site for Oct-4B transcription. *Biosci Rep*, 31(2):109-115. https://doi.org/10.1042/Bsr20100033

Wen KM, Fu ZX, Wu XY, et al., 2013. Oct-4 is required for an antiapoptotic behavior of chemoresistant colorectal cancer cells enriched for cancer stem cells: effects associated with STAT3/survivin. *Cancer Lett*, 333(1):56-65. https://doi.org/10.1016/j.canlet.2013.01.009

Wong MMT, Chan HY, Aziz NA, et al., 2021. Interplay of autophagy and cancer stem cells in hepatocellular carcinoma. *Mol Biol Rep*, 48(4):3695-3717. https://doi.org/10.1007/s11033-021-06334-9

Wu Q, Wu Z, Bao CY, et al., 2019. Cancer stem cells in esophageal squamous cell cancer (review). *Oncol Lett*, 18(5):5022-5032. https://doi.org/10.3892/ol.2019.10900

Xie WW, Yu J, Yin YJ, et al., 2022. OCT4 induces EMT and promotes ovarian cancer progression by regulating the PI3K/AKT/mTOR pathway. *Front Oncol*, 12:876257. https://doi.org/10.3389/fonc.2022.876257

Yang F, Xu J, Tang L, et al., 2017. Breast cancer stem cell: the roles and therapeutic implications. *Cell Mol Life Sci*, 74(6):951-966. https://doi.org/10.1007/s00018-016-2334-7

Yang PP, Li CS, Zhou Q, et al., 2022. Notum leads to potential pro-survival of OSCC through crosstalk between Shh and Wnt/β-catenin signaling via p-GSK3β. *Int J Biochem Cell Biol*, 153:106316. https://doi.org/10.1016/j.biocel.2022.106316

Yuan FJ, Zhou WB, Zou C, et al., 2010. Expression of Oct4 in HCC and modulation to wnt/β-catenin and TGF-β signal pathways. *Mol Cell Biochem*, 343(1-2):155-162. https://doi.org/10.1007/s11010-010-0509-3

Zhan T, Rindtorff N, Boutros M, 2017. Wnt signaling in cancer. *Oncogene*, 36(11):1461-1473. https://doi.org/10.1038/onc.2016.304

Zhang JM, Wei K, Jiang M, 2018. OCT4 but not SOX2 expression correlates with worse prognosis in surgical patients with triple-negative breast cancer. *Breast Cancer*, 25(4):447-455. https://doi.org/10.1007/s12282-018-0844-x

Zhang L, Meng X, Zhu XW, et al., 2019. Long non-coding RNAs in oral squamous cell carcinoma: biologic function, mechanisms and clinical implications. *Mol Cancer*, 18:102. https://doi.org/10.1186/s12943-019-1021-3

Zhang QZ, Shi SH, Yen Y, et al., 2010. A subpopulation of $CD133^+$ cancer stem-like cells characterized in human oral squamous cell carcinoma confer resistance to chemotherapy. *Cancer Lett*, 289(2):151-160. https://doi.org/10.1016/j.canlet.2009.08.010

Zhao XY, Lu H, Sun Y, et al., 2020. Prognostic value of octamer binding transcription factor 4 for patients with solid tumors: a meta-analysis. *Medicine (Baltimore)*, 99(42): e22804. https://doi.org/10.1097/MD.0000000000022804