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Oral Cancer Stem Cells: A Comprehensive Review

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Abstract: *Oral squamous cell carcinoma (OSCC) remains a major global health challenge, accounting for the majority of head and neck cancers and exhibiting high morbidity and mortality rates. Despite advances in diagnosis and treatment, survival outcomes have improved only marginally, largely due to recurrence, metastasis, and therapeutic resistance. Increasing evidence supports the cancer stem cell (CSC) hypothesis, which proposes that a small subpopulation of tumor cells with stem-like properties drives tumor initiation, progression, and resistance to therapy. This review provides a comprehensive overview of oral cancer stem cells, focusing on their biological characteristics, molecular markers, role in carcinogenesis, and therapeutic implications. Key CSC markers such as CD44, CD133, aldehyde dehydrogenase (ALDH), and pluripotency-associated transcription factors including OCT4, NANOG, and SOX2 are discussed in detail. The interaction between CSCs and the tumor microenvironment (TME), including immune modulation, angiogenesis, and epithelial–mesenchymal transition (EMT), is critically examined. Emerging therapeutic strategies targeting CSCs, including signaling pathway inhibition, marker-based targeting, and combination therapies, are also evaluated. Despite promising advances, challenges such as CSC heterogeneity, plasticity, and resistance mechanisms remain significant barriers. A deeper understanding of CSC biology is essential for the development of more effective and personalized treatment strategies for OSCC.*

Keywords: *Oral cancer, cancer stem cells, SOX-2, OCT4, CD44, CD133, ALDH, tumor microenvironment, targeted therapy*

I. Introduction:

Oral squamous cell carcinoma (OSCC) constitutes approximately 90% of all oral malignancies and represents a significant global public health concern. According to recent epidemiological data, the burden of oral cancer continues to rise, particularly in developing countries, due to risk factors such as tobacco use, alcohol consumption, and human papillomavirus (HPV) infection [1–5]. Despite advancements in surgical techniques, radiotherapy, and chemotherapy, the overall five-year survival rate for OSCC remains around 50–60%, largely due to late diagnosis, recurrence, and metastasis [5].

In recent years, the cancer stem cell (CSC) theory has emerged as a pivotal concept in understanding tumor biology. CSCs are a small subset of tumor cells that possess the ability to self-renew, differentiate, and initiate tumor formation. These cells are thought to play a central role in tumor heterogeneity, progression, metastasis, and resistance to conventional therapies [6–8]. In OSCC, CSCs have been identified using various molecular markers and functional assays, highlighting their clinical significance.

This review aims to provide a comprehensive and updated overview of oral CSCs, including their defining characteristics, identification markers, role in oral carcinogenesis, and therapeutic implications.

II. Biological Characteristics of Oral Cancer Stem Cells:

2.1 Self-Renewal

Self-renewal is a defining feature of CSCs, enabling them to maintain the tumor population over time. This process is regulated by several key signaling pathways, including Wnt/β-catenin, Notch, and Hedgehog pathways, which are also involved in normal stem cell biology [10,11]. Dysregulation of these pathways contributes to uncontrolled proliferation and tumor growth.

2.2 Differentiation Potential

CSCs possess the ability to differentiate into multiple cell lineages, generating heterogeneous tumor cell populations. This differentiation capacity contributes to tumor complexity and complicates therapeutic targeting [8].

2.3 Tumorigenicity
One of the hallmark features of CSCs is their high tumorigenic potential. Studies have demonstrated that even a small number of CSCs can initiate tumor formation in immunocompromised animal models, whereas a larger number of non-CSCs fail to do so [12].
2.4 Resistance to Therapy
CSCs exhibit resistance to conventional therapies such as chemotherapy and radiotherapy. Mechanisms underlying this resistance include enhanced DNA repair capacity, overexpression of drug efflux transporters, resistance to apoptosis, and quiescent cell cycle status [7,13]. This resistance contributes significantly to tumor recurrence and poor prognosis.

III. Molecular Markers of Oral Cancer Stem Cells:

3.1 CD44
CD44 is a cell surface glycoprotein involved in cell adhesion and migration. It is one of the most widely used markers for identifying CSCs in OSCC. CD44-positive cells exhibit increased tumorigenicity, invasiveness, and resistance to therapy [12].
3.2 CD133
CD133 (prominin-1) is another important CSC marker associated with poor clinical outcomes. CD133-positive cells demonstrate enhanced sphere-forming ability, tumor initiation capacity, and resistance to chemotherapy [14].
3.3 Aldehyde Dehydrogenase (ALDH)
ALDH activity is considered a functional marker for CSCs. ALDH-positive cells are associated with increased clonogenicity, tumorigenicity, and resistance to oxidative stress and chemotherapy [13,15].
3.4 Pluripotency Markers (OCT4, NANOG, SOX2)
Transcription factors such as OCT4, NANOG, and SOX2 are essential for maintaining stemness and pluripotency. Their overexpression in OSCC has been linked to tumor aggressiveness, metastasis, and poor prognosis [16–18].

SOX2 (Sex Determining Region Y-Box 2)
SOX2 is a key transcription factor involved in embryonic development and maintenance of pluripotency. In OSCC, SOX2 overexpression has been strongly associated with enhanced tumor aggressiveness, poor differentiation, and increased metastatic potential.
Mechanistically, SOX2 regulates multiple signaling pathways including **Wnt/β-catenin, Notch, and Hedgehog**, which are essential for CSC maintenance and self-renewal. It also promotes epithelial–mesenchymal transition (EMT), thereby facilitating tumor invasion and metastasis.
Studies have demonstrated that SOX2-positive CSCs exhibit increased sphere-forming ability, resistance to chemotherapy, and enhanced tumorigenicity. Furthermore, SOX2 contributes to immune evasion by modulating cytokine signaling within the tumor microenvironment.
Recent molecular investigations suggest that SOX2-associated signaling networks regulate key biological phenotypes of cancers, making it a promising therapeutic target [17,18].

OCT4 (Octamer-Binding Transcription Factor 4)
OCT4 is a master regulator of pluripotency and is essential for maintaining the self-renewal of embryonic stem cells. In OSCC, aberrant expression of OCT4 has been linked to poor prognosis, increased tumor recurrence, and resistance to therapy.
OCT4 functions by regulating downstream genes involved in stemness and survival. It often acts synergistically with SOX2 and NANOG to maintain the CSC phenotype.
Clinical studies have demonstrated that OCT4-positive cells in OSCC are associated with higher tumor grade and increased metastatic potential. Additionally, OCT4 expression correlates with resistance to apoptosis and enhanced DNA repair mechanisms, contributing to treatment failure [16].

NANOG
NANOG is another critical transcription factor involved in maintaining pluripotency and self-renewal. Its overexpression in OSCC has been correlated with increased tumor aggressiveness, poor differentiation, and unfavorable prognosis.
NANOG functions in concert with SOX2 and OCT4 to regulate gene expression patterns that sustain CSC characteristics. It enhances clonogenicity, tumorigenicity, and resistance to chemotherapy.
Importantly, NANOG has been shown to promote EMT and contribute to metastasis. Elevated NANOG expression is also associated with increased resistance to radiotherapy, further highlighting its clinical significance [16].

Combined Role of SOX2, OCT4, OCT2, and NANOG

These transcription factors do not act independently but form a **core regulatory network** that maintains CSC properties. Their coordinated expression ensures sustained self-renewal, inhibition of differentiation, and adaptation to environmental stress.

Dysregulation of this network leads to:

- Enhanced tumor initiation and progression
- Increased metastatic potential
- Resistance to chemotherapy and radiotherapy
- Poor clinical outcomes

Targeting this transcriptional network represents a promising therapeutic strategy for eliminating CSCs and improving OSCC prognosis.

IV. Role of CSCs in Oral Carcinogenesis:

4.1 Initiation and Premalignant Progression

CSCs are believed to originate from normal stem cells or progenitor cells that undergo genetic and epigenetic alterations. These transformed cells contribute to the progression of oral potentially malignant disorders (OPMDs) into invasive carcinoma [9].

4.2 Tumor Microenvironment (TME)

The TME plays a critical role in regulating CSC behavior. Components such as cancer-associated fibroblasts, immune cells, extracellular matrix, and cytokines interact with CSCs to promote tumor growth, angiogenesis, and immune evasion [19].

4.3 Epithelial–Mesenchymal Transition (EMT)

EMT is a biological process that enables epithelial cells to acquire mesenchymal characteristics, enhancing their migratory and invasive capabilities. CSCs are closely associated with EMT, which facilitates metastasis and contributes to therapeutic resistance [20].

4.4 Metastasis and Recurrence

CSCs are implicated in metastatic dissemination due to their ability to survive in circulation and colonize distant organs. Their resistance to therapy further contributes to tumor recurrence [7].

V. Therapeutic Targeting of Oral Cancer Stem Cells:

5.1 Marker-Based Targeting:

Therapies targeting CSC-specific markers such as CD44 and CD133 aim to selectively eliminate tumor-initiating cells while sparing normal cells. Monoclonal antibodies and targeted drug delivery systems are being explored in this context [14].

5.2 Signaling Pathway Inhibition:

Targeting dysregulated signaling pathways such as Wnt/β-catenin, Notch, Hedgehog, and c-Met represents a promising therapeutic strategy. Inhibition of these pathways can disrupt CSC self-renewal and survival [10,21].

5.3 Targeting the Tumor Microenvironment:

Modulating the TME to disrupt CSC niches is another emerging approach. Strategies include targeting stromal cells, angiogenesis, and immune checkpoints to inhibit CSC maintenance [19].

5.4 Exosome-Based Therapy:

Exosomes derived from mesenchymal stem cells have been investigated as delivery vehicles for therapeutic agents, including microRNAs and drugs targeting CSCs [22].

5.5 Combination Therapy:

Combining CSC-targeted therapies with conventional treatments such as chemotherapy and radiotherapy may enhance treatment efficacy and reduce recurrence rates [11].

VI. Challenges and Future Directions:

Despite significant progress in CSC research, several challenges remain:

Heterogeneity: CSC populations vary within and between tumors, complicating marker identification and therapeutic targeting.

Plasticity: Non-CSCs can acquire stem-like properties under certain conditions, limiting the effectiveness of CSC-targeted therapies.

Resistance Mechanisms: CSCs employ multiple mechanisms to evade therapy, necessitating multi-targeted approaches.

Future research should focus on identifying novel and specific CSC markers, understanding CSC-TME interactions, and developing personalized therapeutic strategies. Advances in genomics, proteomics, and single-cell sequencing technologies are expected to provide deeper insights into CSC biology.

VII. Conclusion:

Cancer stem cells play a fundamental role in the pathogenesis, progression, and therapeutic resistance of oral squamous cell carcinoma. Their unique biological properties make them critical targets for novel therapeutic strategies. Although significant progress has been made in understanding CSC biology, challenges such as heterogeneity and resistance remain. Continued research is essential to translate these findings into clinical applications that improve patient outcomes and survival rates.

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