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REVIEW

Oral squamous cell carcinoma: Insights into cellular heterogeneity, drug resistance, and evolutionary trajectories

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Abstract Oral squamous cell carcinoma (OSCC) can lead to metastasis and high mortality rates known for its aggressive and invasive properties. Currently, primary treatment options of surgical resection, chemotherapy and radiotherapy have many therapeutic limitations for OSCC patients due to its dynamic evolutionary pathways and the development of resistance to conventional therapies. Moreover, previous studies fail to emphasize the roles of cellular heterogeneity, drug resistance, and evolutionary trajectories in OSCC. This review explores the intricate tumor microenvironment landscape of OSCC, focusing on the cellular heterogeneity, drug resistance, and evolutionary trajectories as well as genetic, epigenetic, and environmental risk factors contributing to the OSCC progression. Tumor heterogeneity arises from environmental exposures (e.g., tobacco, HPV infection, dietary carcinogens) that drive clonal evolution, creating subpopulations of cells with distinct mutational profiles and therapeutic vulnerabilities. Recent advances in in the precision medicine and combination therapy of OSCC paves the way for innovative therapeutic strategies, such as targeting molecular subclones through real-time monitoring and leveraging computational models to predict treatment response. By recognizing tumor heterogeneity as both a driver of therapeutic resistance and a therapeutic target, precision medicine frameworks can integrate environmental risk factor data, molecular profiling, and early detection tools to optimize outcomes. This review underscores the necessity for a multidisciplinary approach to understand and combat the complexity of OSCC, proposing directions for future research to enhance diagnosis and treatment efficacy.

Keywords Oral squamous cell carcinoma (OSCC) · Cellular heterogeneity · Drug resistance · Evolutionary trajectories

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Introduction

Oral squamous cell carcinoma (OSCC) is defined as an important global health burden in head and neck disease due to its poor prognosis and high mortality with 177,000 new deaths per year (Sun, et al. 2023). According to data collected by the Global Cancer Observatory (GCO), there were 377,713 new cases of OSCC were reported worldwide in 2020, with the majority occurring in Asia (Tan, et al. 2023). Many risk factors, including smoking, betel quid consumption, alcohol consumption, poor nutritional status, and dust, cause chronic inflammation, HPV infection, poor oral hygiene, immune system dysfunction, heritable factors, and sex (Batistella, et al. 2022, Hecht and Hatsukami 2022, D'Souza and Addepalli 2018) (Fig. 1). Globally, an estimated 30.8% of OSCC cases were attributable to smokeless tobacco or areca nut consumption in 2022 (Rumgay, et al. 2024). The 5-year survival rate for OSCC patients still holds at a grim approximate of 50%, with some slight increase due to advances in diagnosis and treatments (Zanoni, et al. 2019). The usual culprit for this grave prognosis is the advancement of the disease stage upon diagnosis and complex biological behavior of the tumor.

Understanding the biological mechanisms of oral squamous cell carcinoma is crucial for improving clinical outcomes. Key challenges include cellular heterogeneity, drug resistance, and difficulties in disease management (Galeano Niño, et al. 2022). Cellular heterogeneity refers to a tumor's coexistence of several populations of cells, each maintaining a different genetic and phenotypic profile. It is this cellular heterogeneity that not only gives a problem in making an accurate diagnosis and prognosis but also accounts for the variable response to therapy amongst patients with OSCC (Peng, et al. 2021, Bano, et al. 2022, Adami, et al. 2017). In recent years, the application of single-cell RNA sequencing (scRNA-seq) has unraveled the cellular heterogeneity within common cancer types. For instance, it has reported that the signatures of macrophages, NK cells, and plasma cells were significantly correlated to survival outcomes in nasopharyngeal carcinoma (Chen, et al. 2020). Recent advancements in scRNA-seq have facilitated the identification of distinct phenotypic and functional subgroups of cancer-associated fibroblasts (CAFs) within the tumor microenvironment (TME), the presence of which is associated with poorer prognosis of OSCC (Zhang, et al. 2024). Computational modeling is another approach for the identification of cellular heterogeneity for various oral tumors, such as UMAP. It shows promising advancements in visualization of prognostic biomarker discovery, which may provide a potential solution to addressing the current limitations in predicting OSCC behaviors (Viet, et al. 2024). Drug resistance in OSCC, whether intrinsic or acquired, remains a formidable obstacle for OSCC treatment. Intrinsic resistance is the pre-existence of certain resistant tumor cells that avoid being killed by the initial treatment attempts. Acquired resistance develops over time as cancerous cells learn and adapt to evade and counter the lethal impacts of therapeutic interventions (Olmedo, et al. 2023). The mechanisms underlying the development of drug resistance are complex and include genetic mutations, epigenetic changes, and alterations in the TME (Meng, et al. 2021, Lin, et al. 2023). These factors influence how tumor cells evolve over the course of the disease and treatment, following Darwinian principles of natural selection. As some cells are eradicated by therapy, others adapt and thrive, leading to the evolution of increasingly resistant and aggressive cancer cell populations. In addition, the evolutionary trajectories of OSCC are shaped by the continuous adaptation of tumor cells to their microenvironment and therapeutic pressures. This dynamic process can be envisioned as a branching tree, where each branch represents a distinct evolutionary path taken by subclones within the tumor. Understanding these trajectories is vital for predicting disease progression and designing effective treatments.

The objectives of this review are threefold. First, it aims to consolidate current knowledge on the genetic and environmental factors contributing to the heterogeneity, drug resistance, and evolutionary dynamics of OSCC. It is interesting to note that, in a few cases, even recent studies have been based on the integration of insights from multiple disciplines and have pursued the building up of a coherent picture of this complex biological landscape. Second, it assesses the impact of these factors on treatment outcomes and disease management. These will be examined in terms of how these challenges provide opportunities for enhancing patient care. Last but not least, this review finally suggests future research directions that may help in the diagnosis, treatment, and management of OSCC. These may range from the creation of new diagnostic tools that are able to identify early signs of resistance to treatment and new therapeutic strategies that can "outsmart" the

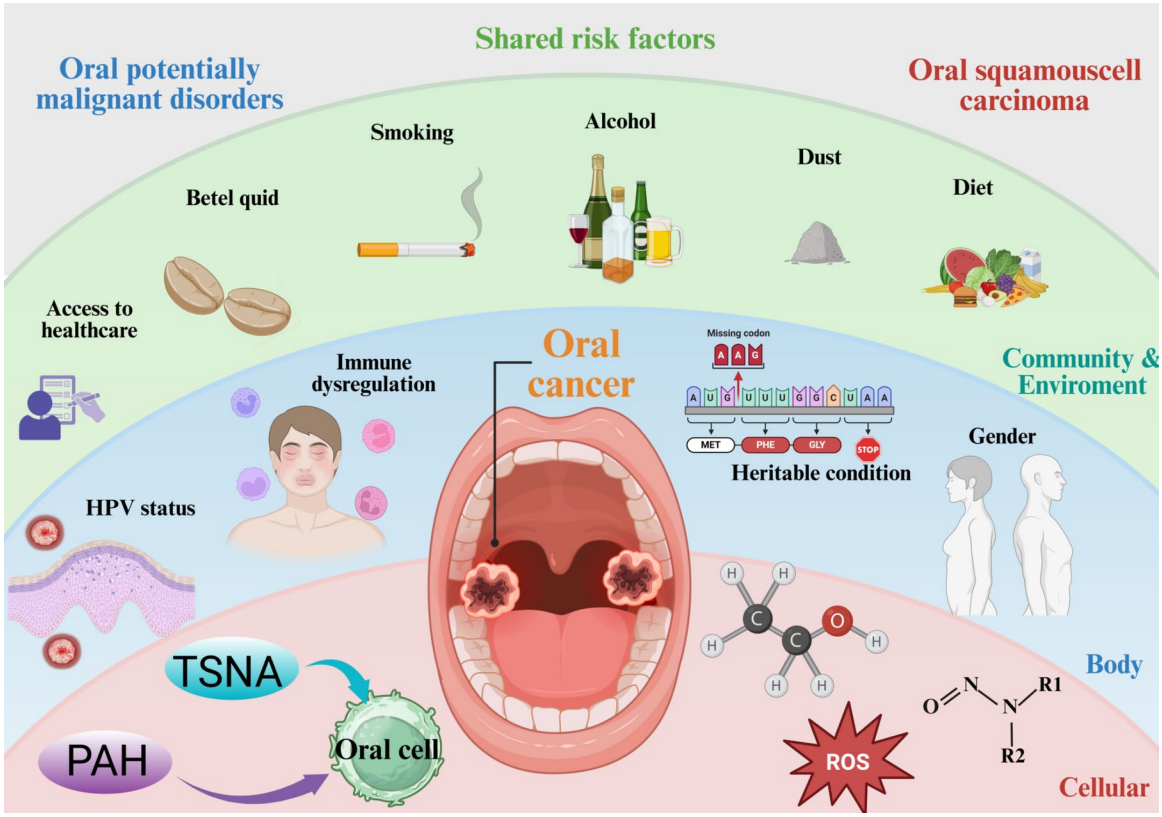

Fig. 1 Key Risk Factors in the Initiation and Progression of OSCC. The initiation and progression of OSCC are influenced by common risk factors such as smoking, alcohol abuse, betel quid chewing, HPV infection, nutritional deficiencies, immune deficiencies, and genetic predispositions

defense response mounted by the tumor cells in their momentous evolutionary fight. Dealing with these critically important aspects, this review hopes that researchers would give a more in-depth and precise understanding of OSCC and thus be able to establish and provide groundwork for those innovations that further can better the survival and quality of life for the patients. Given the evolving nature of OSCC, targeted and adaptive therapies offer promising avenues for overcoming resistance and improving patient outcomes.

Cellular heterogeneity in OSCC

Definition and overview of cellular heterogeneity

Cellular heterogeneity is a fundamental characteristic of many cancers, including OSCC, and it plays a critical role in the disease's progression, treatment response, and prognosis. In the example of OSCC, the heterogeneity of the cells can be observed considering differences in the form of cells, speed of their replication, metabolic activity, or the potential to metastasis (Gangwar, et al. 2022). Such diversity not only makes the diagnosis and classification of the disease difficult but also poses very important challenges for the treatment thereof.

The origins of cellular heterogeneity in OSCC can be traced back to genetic mutations that accumulate in cells over time due to carcinogenic exposures, such as tobacco and alcohol use, or from viral infections like HPV. Research on 64 head and neck squamous cell carcinoma (HNSCC) patients shows that smoking and alcohol abuse significantly alter circulating monocyte and T-cell subset proportions, and aging weakens immunosuppression, compared to healthy volunteers, highlighting the impact of these factors on immune system dynamics in HNSCC. The study

on oral proliferative verrucous leukoplakia (PVL) (Gouvêa, et al. 2010) revealed that DNA aneuploidy and increased expression of minichromosome maintenances 2 (Mcm2), the vital regulator in DNA replication, assessed through ACIS III and immunohistochemistry, correlate with more severe epithelial changes and could predict malignant transformation, highlighting their potential as markers in the aggressive progression of PVL. These mutations confer different capabilities and survival advantages to cells, promoting a Darwinian selection process within the tumor.

Mechanisms contributing to heterogeneity in OSCC

OSCC exhibits significant heterogeneity due to genetic, epigenetic, and environmental influences, leading to diverse tumor cell populations with varying treatment responses. Genetic mutations are the leading cause of the development of cellular heterogeneity in OSCC. A noninvasive genetic assay using next-generation sequencing (NGS) on brushed cells from the oral cavity accurately detects genetically altered fields, including invisible ones, and predicts OSCC development in high-risk individuals by identifying key mutations, offering a powerful tool for early cancer detection and monitoring (Poell, et al. 2023). Thus, the mutation has the potential to give a selective growth advantage of the cells, and therefore promotes clonal expansion and diversity (Abbas, et al. 2020). Mutations in gene TP53 are common in OSCC and result in the formation of cells that are different in their levels of aggressiveness and resistant capacities against apoptosis (Shukla, et al. 2022). The recent study demonstrates that the TP53R172H gain-of-function mutation in OSCC modifies the tumor immune microenvironment (TIME), promoting immune evasion by altering cytokine levels and immune cell infiltration, thus facilitating tumor progression and affecting response to immune therapies (Shi, et al. 2023). Further, genotoxic carcinogens such as tobacco and alcohol exposure turn out to be a key reason for altered cellular behavior, leading to the induction of genetic mutations and metabolic changes that further contribute to heterogeneity (Niaz, et al. 2017). In addition, many intracellular signaling pathways contributed to the complex molecular landscape that drives OSCC development and malignancy, including TP53/RB, p16/Cyclin D1/Rb, EGFR, Wnt/β-catenin, JAK/STAT, NOTCH, PI3 K/AKT/mTOR, MET, and RAS/RAF/MAPK (Fig. 2). For example, increased expression of distal-less homeobox 6 (DLX6) promotes cell growth and prevents cell death in OSCC cells via the EGFR-CCND1 pathway (Liang, et al. 2022). CAFs mediated by high-level ITGB2 activate the PI3 K-AKT-mTOR pathway, enhancing OSCC malignancy progression through NADH oxidation (Zhang, et al. 2020). Through the WNT/β-catenin pathway, DEPDC1 plays a vital role in OSCC progression, driving both metastasis and aerobic glycolysis (Huang, et al. 2023).

The intrinsic genetic diversity within a heterogeneous tumor provides a pool of different genetic mutations. Notably, the development and progression of OSCC are not only caused by irreversible changes in DNA sequence to induce oncogenes activation or inactivation of tumor suppressor genes, but also epigenetic changes(Mesgari, et al. 2023). Tumor cells can modify their epigenomic landscape through processes such as DNA methylation and modifications of histone and non-histone proteins, enabling them to develop various mechanisms of drug resistance as a means to evade anti-cancer therapies.

Therefore, epigenetic alterations were also demonstrated their crucial role in OSCC progression and in the diagnosis and potential treatment due to the heritable modifications in gene expression or cellular traits which do not change DNA sequence (Hema, et al. 2017). They consist of DNA methylation, histone modifications, regulation facilitated by non-coding RNA, chromatin remodeling, and genomic imprinting. Aberrantly DNA methylated tumor suppressor genes SFRP2 and DAPK1 have been revealed in OSCC (Strzelczyk, et al. 2019). MLH1 hypermethylation impairs DNA repair and triggering OSCC by causing changes in genes regulating cell growth and division. DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors have been investigated as possible treatments for OSCC (Yang, et al. 2022). As a result, these DNA methylation patterns can aid in the treatment and early detection of OSCC. However, few studies reported on the relationship between DNA methylation and drug resistance in OSCC cases. Non-coding RNAs (ncRNAs) are RNA molecules that regulate gene expression and cellular processes, including miRNAs and lncRNAs. Epigenetic silencing of miR-137 may contribute to the development of OSCC (Sousa, et al. 2020). In OSCC,

miR-211 is often overexpressed and associated with tumor progression, metastasis, invasion, and poor prognosis (Yan, et al. 2021). The underlying mechanisms for the differential regulation of these miRNAs and miRNAs-based therapies are not well understood. Epigenetic modifications, including DNA methylation and histone modifications, play pivotal roles in OSCC. Aberrant DNA methylation can silence tumor suppressor genes, while alterations in histone modifications and chromatin remodeling influence gene expression patterns associated with drug metabolism and apoptosis (Wang, et al. 2023). DNA hypermethylation of tumor suppressor genes served as prominent diagnostic biomarkers for among OSCC patients, with agents like DNMT and HDAC inhibitors reversing aberrant epigenetic patterns(Agarwal and Jha 2024).

Beyond genetic and epigenetic alterations, another key driver of tumor heterogeneity is the presence of cancer stem cells (CSCs), which generate diverse tumor subpopulations (Erkisa, et al. 2019). They have the ability to self-renew and differentiate into various cell types, which results in distinct subpopulations with different genetic, epigenetic, and phenotypic profiles. These subpopulations exhibit varying degrees of proliferation, differentiation, and resistance to therapies, ultimately driving the complexity and adaptability of the tumor (Han, et al. 2024, Guo, et al. 2024). This cellular diversity contributes to tumor progression, metastasis, and drug resistance, making treatment more challenging. OSCC is known for its high degree of cellular heterogeneity, a characteristic that complicates diagnosis, prognosis, and treatment strategies (Ghiyasimoghaddam, et al. 2024). CSC markers such as ALDH1 have been identified in oral premalignant disorders and OSCC, indicating their potential roles in tumorigenicity and metastasis (Dhumal, et al. 2022). Compared to primary tumors, the proportion of ALDH1-expressing cells was significantly increased in metastases, characterized by higher nodal classification and lower differentiation (Qian, et al. 2013). Therefore, inhibitors may serve as a promising therapeutic strategy for OSCC. Research has demonstrated that CSCs in HNSCC, which includes OSCC, are metabolically inactive compared to differentiated tumor cells, rendering them resistant to conventional therapies, particularly those targeting metabolic pathways. The plasticity of CSCs in OSCC further exacerbates treatment resistance, as they can switch between different phenotypes, including migratory and proliferative states (Biddle, et al. 2011). Moreover, high expression of CSC-associated genes, such as LIMP-2, has been correlated with poor prognosis and resistance to immunotherapy in HNSCC patients (Liu, et al. 2023). This evidence highlights the importance of developing new therapeutic strategies that specifically target CSCs.

Recent studies using single-cell RNA sequencing and other advanced techniques have provided insights into the characterization of CSC populations, revealing the complexity of stem-like cells in the OSCC microenvironment (Johansson and Ueno 2021). These findings underscore the need for better biomarkers and therapeutic targets to overcome the challenges posed by CSC heterogeneity and resistance mechanisms in OSCC (Sadasivam and Subramanian 2020, Vipparthi, et al. 2022). Currently, the development of new CSC-targeted strategies is currently hindered by the lack of reliable markers for the identification of CSCs and the poor understanding of their behavior and fate determinants. A previous study revealed that CCL3 signaling via its receptor is crucial for supporting the CSC phenotype in OSCC cells (Lee, et al. 2021), suggesting the potential CSC-targeted therapies for OSCC. It has been reported that CAFs effectively attract monocytes via the CXCL12/CXCR4 pathway and polarize M2 macrophages, which promote the formation of CSC-like cells from the OSCC, leading to increased OSCC proliferation (Li, et al. 2019). The WNT/β-catenin signaling pathway plays a vital role in cell proliferation, differentiation, and metastasis of OSCC (Zeng, et al. 2022, Hou, et al. 2024). WNT3 promotes chemo-resistance to 5-Fluorouracil in oral squamous cell carcinoma via activating the canonical β-catenin pathway(Zhang, et al. 2024). The Wnt/β-catenin inhibitors have not been developed at present. In conclusion, the unique properties of CSCs, including their ability to drive tumor heterogeneity and resistance to therapy, present significant challenges in treating OSCC. Addressing these challenges requires a deeper understanding of CSC biology and the development of novel, targeted treatment strategies (Byrd, et al. 2019, Reers, et al. 2014).

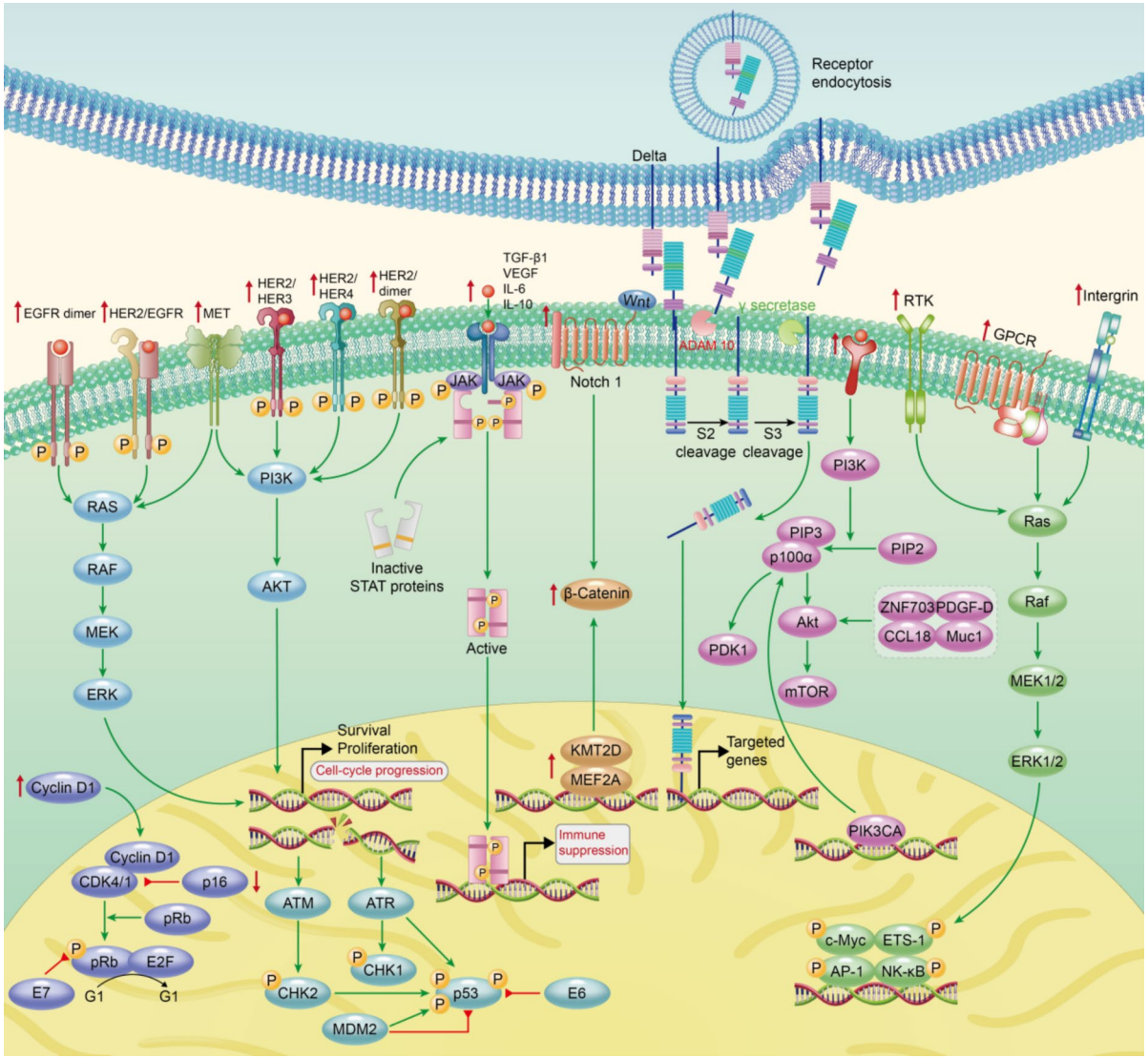

Fig. 2 Genetic Alterations and Key Signaling Pathways Driving OSCC Progression. Genetic alterations in several key signaling pathways, including TP53/RB, p16/Cyclin D1/Rb, EGFR, Wnt/β-catenin, JAK/STAT, NOTCH, PI3 K/AKT/mTOR, MET, and RAS/RAF/MAPK, are instrumental in the progression of OSCC

Impact of cellular heterogeneity on tumor behavior and patient outcomes in OSCC

Cellular heterogeneity greatly affects the tumor behavior in OSCC and the outcome of the patient. The heterogeneous cellular population in OSCC, however, allows different cells within the same tumor to portray different biological behaviors. Some cells may be carrying higher proliferative capacities, while others may be more competent to invade surrounding tissues or the metastatic potential to distant sites. Such a variable susceptibility would imply variable growth rates between different tumors, and hence the growth of the tumor is not even, which may further complicate the predictability and hence treatment for the disease.

Cellular heterogeneity has been posed as one of the most deleterious effects on the efficacy of therapeutic interventions. Diverse cell populations within a tumor may very well respond to treatment in divergent ways, with intrinsically resistant or acquired resistance by

evolutionary pressures induced by the therapy itself. These cells are resistant to the killing of them, giving rise to relapse of the tumor that is further aggressive and refractory. Previous study highlights the role of the long non-coding RNA LINC00152 (CYTOR) in promoting migration, invasion, and epithelial-mesenchymal transition in OSCC, identifies its mechanism via interaction with HNRNPC to stabilize ZEB1 mRNAs, and demonstrates effective CYTOR-targeted suppression using siRNAs encapsulated in nanoscale frameworks to inhibit OSCC metastasis (Zhu, et al. 2022). Variabilities in drug response among patients could, in part, be contributed by heterogeneity of the tumor cells, which often call for a combination of therapies to effectively target different populations of the cell. In this manner, cellular heterogeneity makes the assessment of disease stage and prognosis very complex. Traditional markers of tumor behavior, largely diagnostic and prognostic, may be poor indicators of the full biological spectrum of tumor behavior, considering that not all are expressed by each subclone and some express subclonally, behaving differently from dominants. This might result in underestimation of the aggressiveness of the tumor, its capacity to progress, and therefore optimally affect the planning of the treatment of the tumor; hence, worse patient outcomes.

Evolutionary trajectories in OSCC

The concept of tumor evolution in OSCC

Tumor evolution in OSCC refers to the dynamic and ongoing process through which tumor cells acquire genetic and epigenetic changes over time, enabling them to adapt, survive, and proliferate in varying environmental and therapeutic conditions (Nasir, et al. 2020, Scano, et al. 2022, Gabusi, et al. 2023). This evolutionary process is driven by the principles of Darwinian selection, where genetic diversity within a tumor provides a reservoir from which certain cells can be selected for survival based on their fitness advantages. As OSCC progresses, it continually evolves through mechanisms such as mutation, gene amplification, and chromosomal rearrangements. The ole of the tumor microenvironment needs more specificity. Each of these genetic alterations can confer new properties to the tumor cells, such as increased growth rates, resistance to apoptosis, and the ability to metastasize. Importantly, the selective pressures imposed by the body's immune response and therapeutic interventions can accelerate this evolutionary process. Cells that can evade immune detection or resist treatments will survive and expand, often leading to a more aggressive cancer phenotype (Chen, et al. 2022).

Drivers and techniques in studying evolutionary trajectories of OSCC

OSCC, like many other cancers, undergoes complex evolutionary processes driven by various factors that contribute to its progression and diversity. The rate at which mutations happen within the DNA of tumor cells forms the fundamental driving factor to how OSCC evolves. Mutations within DNA could arise due to replication errors, the influence of carcinogens like tobacco smoke, alcohol, or radiation exposure (Zhu, Wang, Liu, Xu, Zhai, Zhang, Wang, Wang and Liu 2022, Alshahrani, et al. 2021). These mutations generate genetic diversity, serving as the foundation for natural selection in tumor evolution. Indeed, the rapid evolution of some tumor cells, with the acquisition of advantageous traits allowing them to proliferate, invade adjacent tissues, and escape destruction by treatments, has even been linked to high mutation rates. Selective pressures, no doubt, from the tumor microenvironment add to the shaping of the evolutionary path of OSCCs (Chen, Feng, Yan, Zhao, Zhao and Guo 2022, Liu, et al. 2022). Those, possibly, could be pressures from immune surveillance, which may include the selective killing of particular tumor cells by the immune system and therapeutic interventions acting on certain cell populations. These cells, which can escape immune response or become resistant to therapies, are expected to have better survival and therefore outgrow the other cells, initiating an evolution into more aggressive and refractory to treatment tumors. The surrounding environment of the tumor cells forms the blood vessels, immune cells, and fibroblasts, along with extracellular matrix that surrounds the tumor cells. All these have a great impact on the evolution of the cancer. Understanding tumor evolution requires advanced research tools capable of capturing genetic diversity at the cellular level. Below, we discuss key techniques providing insights into OSCC progression.

Single-cell sequencing has revolutionized our understanding of how tumors evolve at the cellular level, revealing the existence of distinct subpopulations

within a tumor that may respond differently to treatment (Peng, Xiao, Rong, Ou, Cai, Liu, Li, Zhang, Wu, Lan, Lin, Li, Ren, Fan and Li 2021). Single-cell RNA sequencing of oral squamous cell carcinoma of the gingivo-buccal region (OSCC-GB) in India reveals distinct malignant cell types and phenotypic shifts in tumors with concomitant oral submucous fibrosis, highlighting unique expression markers and immune-related gene enrichment in cells undergoing partial epithelial-mesenchymal transition and fetal cellular reprogramming, and a diverse and robust T cell presence within the tumor microenvironment (Kurkalang, et al. 2023, Zhi, et al. 2024). This technique can also identify rare cancer cell clones that might drive relapse after treatment, helping in the design of more comprehensive and effective therapeutic strategies. By applying principles from evolutionary biology, phylogenetic analysis helps in reconstructing the lineage relationships between tumor cells based on their genetic similarities and differences. This approach can map how tumor cells have evolved over time and branched into distinct subclones. Hypoxia-induced selective pressures favor aggressive subclones that resist apoptosis and promote metastasis. Such analysis often uses data from both bulk and single-cell sequencing to provide a detailed picture of the tumor's evolutionary history and predict future evolutionary trajectories.

Together, these drivers and techniques enable a more nuanced understanding of the dynamics of OSCC progression. The analysis of mutation rates, selective pressures, and the tumor microenvironment are critical factors in understanding cancer evolution. Modern techniques such as single-cell sequencing and phylogenetic analysis enhance our ability to trace these changes even at the stage of their onset and development in the body, thus allowing for potential pathways of targeted intervention and more individualized approaches to cancer treatment. Understanding these evolutionary dynamics is essential for designing adaptive treatment strategies, such as combination therapies that target both dominant and resistant subclones.

Drug resistance in OSCC

Therapeutic strategies and resistance in OSCC

OSCC treatment involves a multifaceted approach that combines surgery, radiation therapy, chemotherapy, and targeted therapies. Drug resistance has become a major obstacle in the treatment of OSCC, seriously affecting the prognosis of patients. In the treatment of OSCC, the emergence of drug resistance involves multiple levels of mechanisms, including not only the genetic variations in the cancer cells themselves but also factors closely related to the factors of the tumor microenvironment. Despite advancements in these treatment modalities, resistance to therapies remains a significant challenge, impacting patient outcomes and survival rates.

Surgery is often the first-line treatment for OSCC, especially in its early stages. The goal is to remove the tumor and a margin of surrounding tissue to ensure all cancerous cells are excised. While surgery can be highly effective in removing localized tumors, it is less effective against metastatic disease and cannot address microscopic disseminations, which may lead to recurrence. Radiation therapy is commonly used in OSCC, either as a primary or adjuvant treatment (Naik, et al. 2022; Kilic and Campbell 2022; Rubin, et al. 2019). It works by damaging the DNA of tumor cells, leading to cell death. However, resistance to radiation can develop, particularly in tumors that possess enhanced DNA repair capabilities or those with hypoxic conditions. Hypoxic tumor cells are more resistant to radiation because the lack of oxygen in these cells renders them less susceptible to radiation-induced damage. Chemotherapy targets rapidly dividing cells and is used to treat OSCC that has a high risk of spreading (Parmar, et al. 2021, de Oliveira, et al. 2021). Common agents include cisplatin, carboplatin, and fluorouracil. Resistance to chemotherapy is a major hurdle, often arising from the ability of tumor cells to efflux drugs, inactivate drug molecules, or repair the drug-induced DNA damage more effectively (Patil, et al. 2020, Furness, et al. 2011). This resistance can be intrinsic from the onset or acquired after initial exposure to chemotherapy, driven by the selection of resistant cell clones.

EGFR (Epidermal Growth Factor Receptor) inhibitors, such as cetuximab, are examples of targeted therapy used in treating OSCC (Van Cutsem, et al. 2023, Driehuis, et al. 2019, Lam, et al. 2019). The RTOG 1016 study found that for HPV-positive oropharyngeal squamous cell carcinoma, radiotherapy plus cetuximab did not meet non-inferiority criteria for overall survival compared to radiotherapy plus cisplatin, with cetuximab also showing higher

progression-free survival and locoregional failure rates, although toxicity levels were similar between the two treatments (Gillison, et al. 2019). In a phase-II study, cetuximab-800 CW showed high sensitivity and negative predictive value for detecting tumor-positive margins in oral squamous cell carcinoma surgery, proving to be well-tolerated and effective for intraoperative margin assessment, with frozen section analysis of fluorescent spots enhancing surgical precision (de Wit, et al. 2023, Krishnan, et al. 2022, Altamura and Borzacchiello 2022). Resistance to targeted therapies typically arises from mutations in the target receptors, activation of alternative growth pathways, or compensatory changes in the tumor microenvironment that help sustain cancer cell survival despite the blockade of the intended targets. Emerging as a promising approach in OSCC treatment, immunotherapy enhances the body's immune response against tumor cells. Checkpoint inhibitors, which release the natural brakes on the immune system, allowing it to attack tumor cells more effectively, have shown promise (Elad, et al. 2022, Vigarios, et al. 2017). Yet, resistance can still occur, often through the tumor cells' ability to camouflage themselves from the immune system or by creating an immunosuppressive tumor microenvironment.

Mechanisms of drug resistance in OSCC

The main types of drug resistance that contribute greatly to the inefficacy of most therapeutic regimens in OSCC can be classified as intrinsic and acquired resistance. Intrinsic or inherent resistance is the pre-existence capability of cancerous cells to resist the effects of either chemotherapy or targeted drugs from the commencement of the treatment. This form of resistance is typically due to genetic mutations, gene amplifications, or altered cellular pathways that exist prior to therapy. Increasing resistance to chemotherapy in OSCC is closely linked to the epithelial−mesenchymal transition (EMT), where EMT-activating transcription factors such as Snail, TWIST, and ZEB activate pathways that not only promote tumor survival and immune evasion but also enhance drug resistance, highlighting the need for advanced therapeutic strategies to combat these mechanisms (Sha, et al. 2021). For example, some cells of OSCC may naturally have high levels of expression for drug efflux pumps, which actively shuttle chemotherapy agents out of the cells, thereby decreasing their cytotoxic effects. Alternatively, some genetic changes can result in the drug target being less sensitive or even non-responsive to its supposed inhibitor. Acquired drug resistance develops over time during treatment as initially sensitive tumor cells undergo genetic or epigenetic changes that enable their survival in the presence of anticancer drugs. This adaptation can happen through various mechanisms, including secondary mutations in the target gene, activation of compensatory signaling pathways, or changes in the tumor microenvironment that provide survival signals to tumor cells. The study identifies a novel miRNA-485-5p/KRT17/integrin/FAK/Src/ERK/β-catenin signaling pathway in OSCC that enhances cancer stemness and drug resistance, suggesting that targeting this pathway could be an effective strategy for overcoming chemoresistance and improving treatment outcomes in OSCC (Jang, et al. 2022). The study identifies a novel miR-365-3p/EHF/KRT16/β5-integrin/c-Met signaling pathway in OSCC, linking high KRT16 expression with poor patient outcomes and demonstrating that targeting this pathway enhances chemosensitivity and reduces cancer cell migration, invasion, and metastasis, suggesting potential therapeutic efficacy for OSCC treatment (Huang, et al. 2019). For example, prolonged exposure to EGFR inhibitors may lead to the activation of alternative growth factor receptors or downstream signaling pathways, allowing the tumor cells to continue proliferating, although one of their primary targets had been effectively blocked (Hata, et al. 2016). These insights underscore the complexity of OSCC treatment and highlight the need for continuous research and development of more effective therapies that can overcome these resistance mechanisms.

The role of TME in influencing drug resistance in OSCC

Cellular heterogeneity in the TME is the key factor that provides a challenging platform for drug resistance in OSCC. Their complex interaction often results in treatment failure and recurrence of cancer. While both M1 and M2 macrophages contribute to tumor-related inflammation, M2 macrophages are more predisposed to fostering angiogenesis, neovascularization, and the activation and remodeling of the stroma(Liu, et al. 2021). TME mainly includes various non-cancerous

cellular elements such as fibroblasts, immune cells, endothelial cells, and a rich extracellular matrix (Li, et al. 2023). Additionally, it encompasses several biochemical and physical factors like cytokines and growth factors, which significantly influence the behavior of tumor cells, particularly their response to therapies. OSCC, an example of a hypoxic tumor, has an internally diverse metabolic environment. For instance, hypoxia triggers cellular responses that activate survival pathways leading to the expression of genes associated with drug resistance (Fig. 3). Hypoxia-inducible factors (HIFs) serve as the primary mediators of the hypoxic response. Under normoxic conditions, the E3 ubiquitin ligase VHL protein facilitates the degradation of HIFα subunits(Greer, et al. 2012). Conversely, during hypoxic conditions, HIFα subunits become stabilized and translocate to the nucleus, where they dimerize with HIFβ and bind to hypoxia response elements (HREs). Furthermore, hypoxia enhances the interaction between Bcl-2 and Twist1, which is associated with poor prognosis in patients with OSCC(Joseph, et al. 2018). There is a notable correlation between hypoxia and epithelial-mesenchymal transition (EMT) in relation to OSCC metastasis and invasion. Hypoxia-induced downregulation of E-cadherin mRNA levels enhances the migratory capacity of OSCC cells(Domingos, et al. 2017). Additionally, HIF-1α inhibits apoptosis and confers increased resistance to chemotherapy and radiotherapy in OSCC, thereby contributing to the disease's aggressiveness. The impact of hypoxia, acidity, and inflammation on tumor evolution is not well detailed.

Furthermore, as a heterogeneous cell population, cancer-associated fibroblasts (CAFs) within the TME secrete growth factors and other signaling molecules that enhance cancer cell survival and promote resistance to treatments such as chemotherapy and radiation (Yuan, et al. 2023, Li, et al. 2022). By altering the extracellular matrix and engaging in significant interactions with cancer cells through secretions like cytokines, chemokines, and growth factors, CAFs contribute to the advancement of cancer and result in worse prognoses for patients (Rastegar-Pouyani, et al. 2024). This environment thus complicates the effectiveness of conventional treatments and underscores the need for innovative approaches that can effectively target these dynamic and adaptive cancer survival mechanisms (Zhao, et al. 2021, Wu, et al. 2021, Lee, et al. 2021). It has demonstrated that CAFs promote cancer stem cell (CSC) growth and tumor progression in OSCC through CXCL-12 and IL-6 secretion. CXCL12 secretion attracts regulatory T cells (Tregs), resulting in Treg infiltration and elevated TGF-β levels in the microenvironment, which fosters a tumor immunosuppressive environment(Liu, et al. 2024). Research has frequently demonstrated a positive link between the activation of the WNT/β-catenin pathway and the aggressive nature of CSCs(Chu, et al. 2024). Treatment with Resveratrol-nanoparticle (Res-NP) effectively reduces CSC proliferation, metastasis, and angiogenesis by inhibiting these cytokines, highlighting its potential as a therapeutic agent against OSCC in various experimental models (Pradhan, et al. 2023). Some studies reveal that the coculture of tumor-associated macrophages (TAMs) and CAFs enhances IL-6 secretion, promoting CSC growth, proliferation, and metastasis in OSCC. Nano-formulated Resveratrol (Res-NP) disrupts this interaction by inhibiting IL-6 production and blocking the IL-6/PD-L1 axis through the JAK2/STAT3 pathway, effectively reducing CSC-associated tumor progression in multiple experimental models (Pradhan, et al. 2024).

For the problem of drug resistance, multidimensional solution strategies need to be adopted. Combination therapy is a key approach. By combining drugs with different mechanisms of action, such as chemotherapy drugs combined with immune checkpoint inhibitors, or small molecule drugs targeting different drug resistance pathways, multiple drug resistance links can be simultaneously acted upon, reducing the possibility of cancer cells developing drug resistance. The development of new drugs is also of crucial importance. For example, ferroptosis inducers designed on the basis of the metabolic characteristics of tumors can induce the death of cancer cells that are resistant to traditional treatments. A nanoparticle drug delivery system can enhance the killing effect of drugs on cancer cells by improving the efficiency of drug delivery. In addition, a liquid biopsy involves the study of circulating cells, cell-free DNA or extracellular vesicles in biofluids to allow for the diagnosis and monitoring of disease, combined with single-cell RNA sequencing (scRNA-seq)(Yekula, et al. 2022). Real-time monitoring of drug resistance markers in patients and dynamic detection of circulating tumor DNA and circulating tumor cells in the blood at single-cell level via liquid biopsy technology are helpful for timely adjustment of treatment plans(Naito and Honda 2023). Moreover, in-depth research on

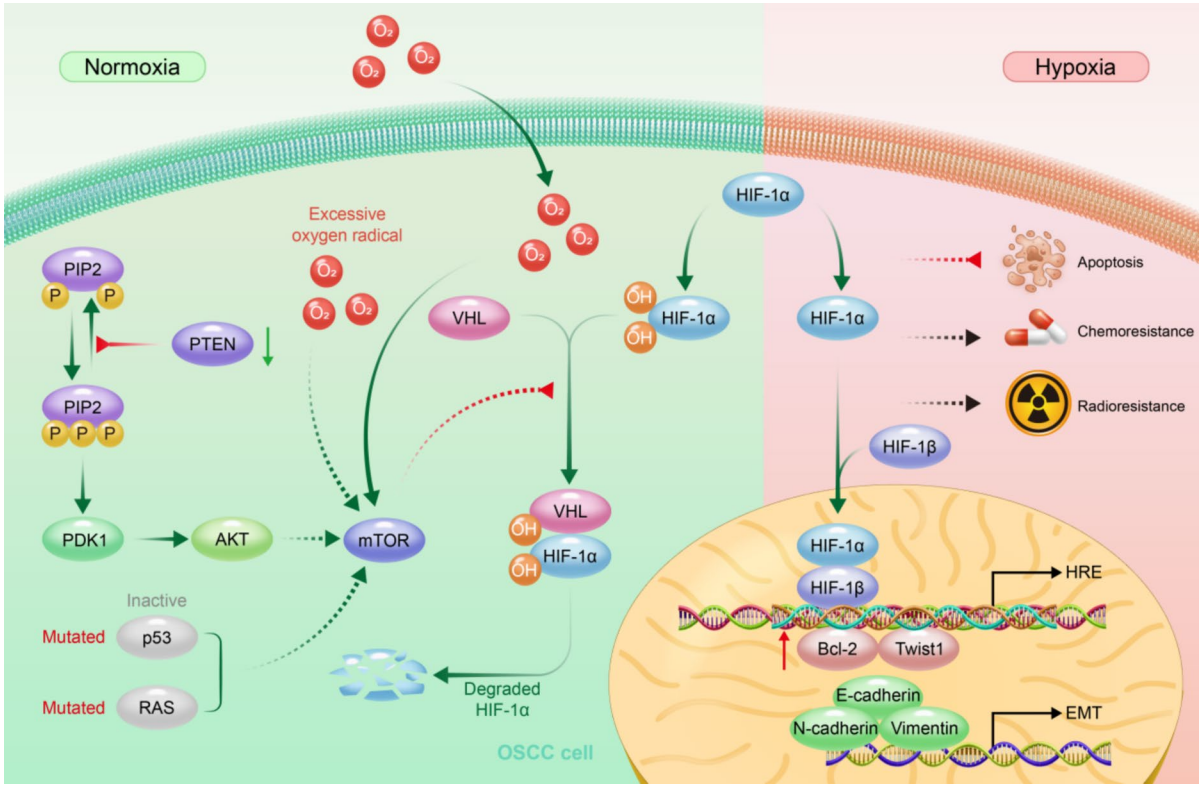

Fig. 3 Hypoxia-Induced Molecular Mechanisms and Drug Resistance in OSCC. In OSCC, hypoxia stabilizes HIFα, which in turn interacts with HIFβ to activate hypoxia-response elements and adapt the tumor environment. This process is further complicated by interactions like Bcl-2 with Twist1, and enhancement of HIFα by the mTOR pathway even in less hypoxic areas

the interaction mechanism between the tumor microenvironment and cancer cells, and targeted regulation of key cells and signaling pathways in the tumor microenvironment, is expected to disrupt the support network for the development of drug resistance and provide new ideas and directions for overcoming the problem of drug resistance in OSCC.

Interconnection between heterogeneity, drug resistance, and evolutionary trajectories

Case studies highlighting the interplay of cellular heterogeneity, drug resistance, and evolutionary trajectories in OSCC

Recent research findings provide compelling insights into how cellular heterogeneity, drug resistance, and evolutionary trajectories interact to complicate the treatment of OSCC. Several case studies have demonstrated these dynamics, showed the clinical implications of these interactions and suggested potential avenues for more effective therapies.

One notable study investigated the genetic landscape of OSCC and found significant intra-tumor genetic heterogeneity. The research revealed that different regions of the same tumor possessed unique mutations and exhibited varied sensitivity to chemotherapy. Specifically, one segment of the tumor harbored the gene mutation, which conferred resistance to cisplatin, a commonly used chemotherapeutic agent in OSCC treatment (Juric, et al. 2018). This segment grew dominantly post-therapy, illustrating how genetic diversity within a tumor can directly influence treatment outcomes and lead to drug resistance (Juric, Rodon, Tabernero, Janku, Burris, Schellens, Middleton, Berlin, Schuler, Gil-Martin, Rugo, Seggewiss-Bernhardt, Huang, Bootle, Demanse,

Blumenstein, Coughlin, Quadt and Baselga 2018). This highlights the critical role of the gene mutation in OSCC, detailing its common genetic alterations such as amplifications and mutations, and their association with disease stage and ethnicity. It underscores the importance of targeting the PI3 K/Akt/mTOR pathway, which is often deregulated in OSCC, suggesting that therapeutic intervention in this pathway could improve early diagnosis and prognosis through personalized treatments. Another study utilized single-cell sequencing to track the clonal evolution of OSCC under therapeutic pressure. It showed that initial treatment with targeted therapy reduced tumor size but also promoted the emergence of a resistant cell clone that was minor before treatment (Choi, et al. 2023). This clone had activated alternative signaling pathways that allowed it to survive despite the drug's action, showcasing the role of evolutionary mechanisms in developing drug resistance. Further research focused on adaptive resistance mechanisms in OSCC involved exposing cancer cell lines to gradually increasing doses of a targeted drug (González-Moles, et al. 2013). The cells adapted by upregulating certain efflux pumps and altering their cell cycle checkpoints. These changes were initially reversible, but some became permanent, indicating that adaptive responses can lead to lasting genetic changes under continuous drug pressure.

Potential therapeutic strategies targeting cellular heterogeneity, drug resistance, and evolutionary trajectories in OSCC

In response to the challenges posed by cellular heterogeneity, drug resistance, and evolutionary trajectories in OSCC, several innovative therapeutic strategies have been developed. These approaches aim to outmaneuver the adaptive capabilities of tumors and improve patient outcomes through more precise and dynamic treatment modalities.

Combination therapies involve using multiple drugs with different mechanisms of action to target various aspects of tumor growth and resistance simultaneously. This strategy loading on nanodrug carriers can effectively reduce the risk of cancer development as a promising avenue for targeted therapeutic approaches in OSCC (Kattimani, et al. 2024, Lai, et al. 2025). Presently, combination therapy is the standard for treating locally advanced OSCC and is effective in improving treatment results. For example, the loading of combinations of cisplatin and chloroquine on polylactic acid (PLA) nanoparticles led to the inhibition of OSCC proliferation through apoptosis and oxidative stress (Silva, et al. 2023). ATO and cisplatin together in OSCC cells led to increased anticancer effects, probably due to the induction of apoptosis through the activation of the caspase-3/7 signaling pathway (Nakaoka, et al. 2014). Proteasome inhibitors have been shown to sensitize OSCC to cisplatin through the ROS/DNA damage/p53 axis (Zheng, et al. 2023). PI3 K/Akt signaling pathway is frequently deregulated in human OSCC, suggesting the potential of PI3 K/Akt/mTOR inhibitors in treating OSCC (Murugan, et al. 2013, Denninghoff, et al. 2020). The current limitation of combination therapies is the lack of more combination projects in addition to combinations with cisplatin. Adaptive therapy is an innovative approach that takes advantage of the evolutionary principles driving tumor growth. Instead of continuous dosing aimed at maximal tumor reduction, adaptive therapy uses treatment schedules that vary in intensity based on tumor response (Fang, et al.). Adaptive therapy aims to inhibit the growth of drug-resistant clones by dynamically monitoring the tumor burden and adjusting the treatment intensity, but it faces many limitations in the treatment of OSCC (Gan, et al. 2024). From a biological perspective, the high degree of cellular heterogeneity within OSCC tumors makes the monitoring and prediction of drug-resistant clones extremely complex. Tumor cells undergo rapid evolution under therapeutic pressure, and the responses of different subclones to treatment vary significantly. Existing detection techniques such as liquid biopsy and imaging methods have difficulty accurately capturing the dynamic changes in all drug-resistant subgroups. The space of the oral cavity is narrow, the boundary between the tumor and the surrounding normal tissues is blurred, and it is easily disturbed by factors such as inflammation and ulcers, making it difficult for imaging examinations to accurately measure the size of the tumor (Keshavarzi, et al. 2017). Moreover, patients with OSCC often have swallowing and language dysfunction, which affects the implementation of tissue biopsy and sample acquisition (Kansy, et al. 2017). It is effective to face with individual response under different dose drugs. Many researchers have foreseen the great potential of using synthetic lethality gene screening

to identify drug combinations and discover specific weaknesses of certain genotypes of cancer. To determine such synthetic lethal interactions, it is important to understand the crosstalk between signaling pathways. The only drug approved for clinical use based on synthetic lethal interactions is the PARP inhibitor, which has been used to treat oral and head & neck cancer (Forster, et al. 2012). Precision medicine in OSCC involves tailoring treatments based on genetic, biomarker, and phenotypic data from individual tumors (Herremans, et al. 2022; Wang, et al. 2018). This approach can enhance the effectiveness of treatment by specifically targeting the molecular abnormalities that drive a particular patient's cancer. For instance, if a tumor exhibits mutations in the EGFR pathway, therapies that specifically inhibit this pathway may be selected. Furthermore, ongoing monitoring of genetic changes in the tumor during treatment can help in adjusting therapies in real-time, countering the evolution of drug resistance.

Clinical implications and future directions

Identification and use of biomarkers related to genetic mutations, expression patterns, and other cellular behaviors specific to OSCC can dramatically improve diagnostic precision and prognostic assessments. Biomarkers can also help guide treatment decisions, leading clinicians to match their patients with therapies that will work best for them on the basis of their tumor characteristics (Feng, et al. 2019) (Fig. 4). For example, personalized medicine, guided by detailed genetic and molecular analysis of individual tumors, allows for treatments tailored to the unique features of each patient's cancer. This may involve customizing drug combinations, dosages, and treatment schedules to increase efficacy and decrease side effects (Chen, et al. 2018). Personalized treatment plans consider the primary tumor characteristics and anticipate potential resistance mechanisms, adjusting treatments as the tumor evolves.

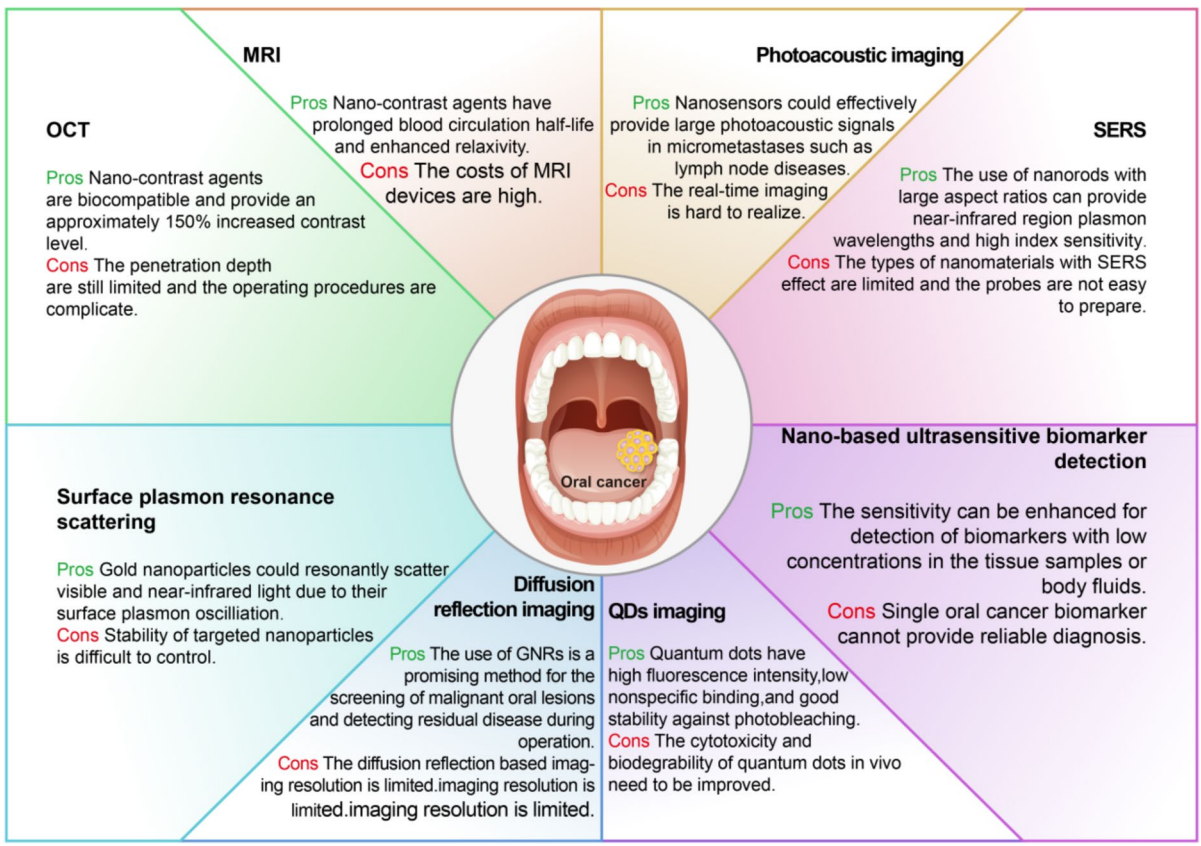

Fig. 4 The pros and cons of different nanotechnology for bioimaging and biomarker detection of OSCC

Future research should focus on designing new therapeutic strategies to avoid or overcome drug resistance. This involves identifying early indicators of resistance, understanding the role of the tumor microenvironment in aiding resistant cells, and designing drugs that target these specific pathways. Early detection significantly improves the prognosis for OSCC(Khurshid, et al. 2018). Research aimed at finding early biomarkers, improving imaging techniques, and developing less invasive testing methods could lead to much earlier diagnosis and treatment. This integration requires advances in bioinformatics and systems biology to effectively interpret complex datasets and translate these into practical treatment strategies.

Effective prevention strategies for OSCC focus on reducing exposure to known risk factors and promoting protective behaviors. Smoking and alcohol cessation programs are critical, as tobacco use (including smokeless forms like betel quid) and excessive alcohol consumption synergistically drive carcinogenesis (Kumar, et al. 2016). Public health policies, such as taxation, advertising bans, and smoke-free laws, further curb tobacco-alcohol use. HPV vaccination is a promising preventive tool, as HPV16/18 infections account for a rising proportion of oropharyngeal cancers (Aragón-Niño, et al. 2023). Public awareness campaigns and expanded access to vaccination in low-resource settings are essential to maximize impact. Dietary interventions emphasize reducing intake of processed meats, salted fish, and alcohol while increasing consumption of antioxidant-rich foods that combat oxidative stress and inflammation. The Mediterranean diet, rich in fiber and polyphenols, shows potential for protection (Meurman 2010). Additionally, limiting sugar and refined carbohydrates may mitigate chronic inflammation and microbiome dysbiosis linked to oral carcinogenesis (Cueva, et al. 2020). Combining these measures with early screening (e.g., oral exams for high-risk populations) and public education on oral hygiene creates a comprehensive approach to reduce the incidence of OSCC.

Discussion and conclusion

Neoplasms remain the main killer worldwide (Zhang, et al. 2023, Hu, et al. 2021, Li, et al. 2023, Wu, et al. 2020). The research into cellular heterogeneity, drug resistance, and evolutionary trajectories in OSCC represents a transformative shift in our understanding and treatment of this complex disease. The interaction among the cellular heterogeneity, drug resistance, and evolutionary trajectories significantly affects the clinical prognosis. Cellular heterogeneity drives evolution by generating drug-resistant subgroups, and evolutionary pressure further intensifies heterogeneity. The evidence further indicates that the genetic heterogeneity of the tumor already exists in the early lesion and may predict the risk of its malignant transformation. This evolutionary dynamic suggests that dynamic monitoring of tumor clonal evolution is crucial for optimizing treatment strategies. By dissecting the underlying mechanisms that drive OSCC's behavior and response to therapy, significant strides have been made in tailoring treatment approaches that address the individual characteristics of each patient's tumor. This review discusses the implications of these findings and the future directions that could potentially revolutionize patient care in the field of oncology.

Chronic tobacco and alcohol use constitute two major risk factors of OSCC, while chronic inflammation, viral infections (HPV virus), betel quid chewing and genetic predisposition are supplementary factors that contribute towards its pathogenesis. The use of tobacco has association with nonspecific global hypomethylation in OSCC. Therefore, it is vital to perform personalized intervention of environmental risk factors to prevent the presence of OSCC. Betel quid, chewed by millions globally, contains alkaloids like arecoline that induce oxidative stress, DNA strand breaks, and chromosomal instability(Wang, et al. 2022). Air pollution, particularly particulate matter, dust, or smoke, delivers carcinogenic polycyclic aromatic hydrocarbons (PAHs) and heavy metals (e.g., arsenic) into the oral mucosa, which induce ROS and activate NF-κB pathways to promote the development of OSCC(Chen, et al. 2020). Dietary factors, beyond alcohol and tobacco, include processed meats (nitrosamines) and charred foods (heterocyclic amines), which not only damage DNA but also alter gut microbiota, influencing oral immunity via the gut-mouth axis. Emerging evidence suggests high sugar intake may promote oral dysbiosis, creating a pro-carcinogenic microenvironment through chronic inflammation(Zaccone, et al.

2022). The introduction of biomarkers and personalized treatment plans based on detailed molecular and genetic profiling has been a pivotal development. Biomarkers have facilitated the identification of specific pathways and mutations involved in cancer progression and resistance, allowing for targeted therapy approaches that are more precise and effective(D'Souza and Addepalli 2018, Kaur, et al. 2018, Fang, et al. 2025). Personalized treatment plans, adjusted to the genetic makeup of the tumor and its evolutionary potential, offer a promise of higher efficacy and lower toxicity, reflecting the shift from a one-size-fits-all approach to more nuanced and patient-specific strategies(Lai, Zhao, Shi, Xing, Li, Jia and Lin 2025). Addressing these underrecognized risks requires multidisciplinary strategies, integrating molecular epidemiology and public health interventions to mitigate OSCC burden.

However, the challenge of drug resistance remains a significant hurdle. Despite advances in understanding the genetic basis of resistance, OSCC's ability to adapt and evolve continues to complicate treatment. Studies that explore the interaction between tumor cells and their microenvironment can unveil new targets for therapy and strategies to prevent the emergence of resistance. Early detection is another critical area requiring more attention (Fang, Liu, Du, Jiang, Gao, Wang, Chi, Shi and Zhao). The prognosis for OSCC significantly improves with early diagnosis, yet many patients are diagnosed at advanced stages (Abati, et al. 2020). Enhanced screening techniques, including non-invasive methods like liquid biopsies, could lead to earlier detection and treatment, potentially improving survival rates. The integration of data from genomics, proteomics, and clinical assessments is also crucial. This comprehensive approach can lead to a deeper understanding of OSCC's behavior and resistance mechanisms, facilitating the development of adaptive treatment plans that can be modified in real time as the tumor evolves.

In a word, while challenges remain, the potential for improving the management and outcomes of OSCC through research into cellular heterogeneity, drug resistance, and evolutionary trajectories is immense. Continued innovation and collaboration in research and clinical practice are crucial for translating these insights into more effective and personalized therapies. Future research needs to focus more on the mechanisms of resistance, especially how the tumor microenvironment contributes to this phenomenon. The adaptive clinical trials also represent a promising future direction, which evolve based on the responses observed in their participants, can accelerate the development of new drugs and treatment strategies. In addition, personalized treatment strategies integrating multi-omics data and organoid models may become a breakthrough direction. For example, through organoid drug sensitivity tests and patient genomic analysis, combined therapies targeting heterogeneity and drug resistance mechanisms can be customized. In addition, targeting the interaction network between the tumor microenvironment (such as CAFs or immune cells) and cancer cells is expected to block the survival signals of drug-resistant clones, thereby improving the prognosis of patients with OSCC.

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Declarations

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