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Review Article

Biological Mechanisms Driving Chemoresistance in Oral Squamous Cell Carcinoma (OSCC): A Review

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ABSTRACT

Drug resistance continues to be a major barrier to the successful treatment of Oral Squamous Cell Carcinoma (OSCC). Numerous processes, including the upregulation of efflux transporters, alterations in drug metabolism, activation of survival pathways like PI3K/Akt, NF-κB, and Wnt/β-catenin, and the Epithelial-Mesenchymal Transition (EMT), are responsible for chemoresistance. By maintaining tumour heterogeneity and self-renewal, Cancer Stem Cells (CSCs) further foster resistance. Among these, activation of pro-survival signaling and CSC-mediated resistance appear most critical. Current research focuses on overcoming these mechanisms through nanocarrier-based drug delivery, gene silencing, autophagy modulation, and targeted inhibition of resistance pathways. Immunotherapeutic approaches, including CAR-T cell therapy combined with checkpoint inhibitors, show encouraging potential. A better understanding of these dominant resistance mechanisms and evidence-based therapeutic strategies is essential to improve clinical medical outcomes in OSCC.

Keywords: Chemoresistance, Immunotherapy, Molecular Targets, Nanoparticle Delivery, Oral Cancer, Precision Medicine.

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INTRODUCTION

With a high rate of death and morbidity, oral cancer is a major health concern on a global scale. Understanding the basic pathogenetic mechanisms that underlie the development of oral cancer is necessary to reduce them (Ramadoss *et al.*, 2024). This form of cancer is the sixth most prevalent worldwide and the third most common in India. Malignancies of the buccal cavity, lips, oropharynx, hypopharynx, and larynx are referred to as mouth and oral cancers (Anwar *et al.*, 2024). In terms of incidence, oral and lip malignancies are ranked sixteenth worldwide (Bohra *et al.*, 2023). The frequency of head and neck cancer is expected to rise by 30% by 2030. Oral and lip cancers are major global health concern, with an expected 188,230 fatalities and 389,485 new diagnoses in 2022 (Bharatwaj *et al.*, 2024). Furthermore, general information about how this type of cancer develops is lacking and its risk factors in developing nations. The fact that over half of participants in a poll conducted in Beijing in 2018-2019 were unaware of this type of malignant tumour should raise concerns (Zhou *et al.*, 2022). In wealthy countries, where 81% of people are aware of oral cancer, the situation is better (Kawecki *et al.*, 2019). It is an essential component that can prevent up to 46% of cases of oral cancer (Bozec *et al.*, 2016). It is particularly prevalent in regions with high rates of alcohol and tobacco use, such as parts of Europe and South Asia. Raising awareness of risk factors such cigarette smoking, poor dental hygiene, and a low-nutritional diet is also a crucial preventive step (Gupta *et al.*, 2017). The majority of Oral cancer cases are Squamous Cell Carcinomas (OSCC), which often present at advanced stages, leading to poor survival rates. Despite improvements in medical care, such as radiation, chemotherapy, and surgery, chemoresistance remains a significant barrier to improving patient outcomes, contributing to high recurrence rates and mortality (Harini *et al.*, 2024). When surgery is not an option, chemotherapy may be administered as the main treatment as an adjuvant postoperative therapy, concomitant chemoradiotherapy, or induction chemotherapy prior to definitive treatment (Pfister *et al.*, 2024). To achieve the greatest possible cancer-killing effects, the gold standard platinum-based chemotherapy treatment consists of administering cisplatin or carboplatin every three to four weeks up to the Maximum Tolerated Dosage (MTD) of 100 mg/m2. Nevertheless, MTD treatment is linked to systemic toxicity and requires three to four weeks of drug-free time to allow for patient recuperation. Another concerning point is that platinum resistance can be induced by the genomic evolution of cancer cells (Sethuraman *et al.*, 2023). By concentrating on quickly dividing

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cancer cells and shrinking tumour size, it is frequently used in conjunction with radiotherapy (chemoradiation) to increase treatment efficacy. Additionally, chemotherapy can increase survival rates and manage metastases. However, the development of chemoresistance often diminishes the effectiveness of chemotherapy, limiting long-term success and highlighting the need for new approaches to address this issue in the treatment of oral cancer. The 30% ineffectiveness problem for common treatments (Tan *et al*., 2022; Harris *et al*., 2022; Ni *et al*., 2021), such as immunotherapy (Evdokimova *et al*., 2022), chemotherapy (Hattinger *et al*., 2023), inhibitory therapy (Li *et al*., 2022), and surgery (Clapp *et al*., 2022), which results in the development of malignant tumours (Yeo *et al*., 2022), has been attempted to be addressed by researchers and medical professionals for nearly 40 years. Despite the numerous trials, no noticeable progress has been made. This results from immunotherapy on tumorigenesis (Guo *et al*., 2023), which, with prolonged treatments (Fazeli *et al*., 2022; Shahpouri *et al*., 2023; Zheng *et al*., 2023), develops severe immune suppression and chemoresistance. Furthermore, the intrinsic and acquired nature of chemoresistance in the Tumour Microenvironment (TME) causes the therapy's progression to finally stop (Lopez-Otin *et al*., 2022). Therefore, increasing the use of more effective treatments with greater cure rates is necessary to overcome this main obstacle (Khadembaschi *et al*., 2022). One of the biggest challenges in treating oral cancer is chemoresistance. This significantly impairs the effectiveness of standard treatments like chemotherapy, increases the chance of recurrence, and decreases patient survival. The Epithelial-Mesenchymal Transition (EMT), drug efflux, and DNA repair and changes in cell death pathways are some of the ways that cancer cells become resistant. Consequently, tumours lose their ability to respond to therapy, which causes the disease to worsen and spread (Priyadharsini *et al*., 2025). Understanding the underlying mechanisms of chemoresistance is necessary to develop targeted ways to improve therapeutic outcomes and prognosis for patients with oral cancer. This study aims to investigate practical remedies and offer a thorough description of the mechanisms driving chemoresistance in oral cancer. By examining recent research on drug resistance pathways like drug efflux, EMT, and survival signaling as well as cutting-edge therapeutic approaches like targeted therapies and combination treatments, this review aims to highlight advancements that can improve the efficacy of oral cancer treatments and reduce recurrence rates succinct without altering the references

MATERIALS AND METHODS

This review adopts a narrative approach supported by a structured literature search to provide an evidence-based overview of drug resistance and emerging therapies in Oral Squamous Cell Carcinoma (OSCC). Relevant studies published were identified through PubMed, Scopus, Web of Science, and Google Scholar using keywords such as “oral squamous cell carcinoma,” “drug resistance,” “targeted therapy,” “tumor microenvironment,” “cancer stem cells,” “Epithelial-Mesenchymal Transition (EMT),” and “nanocarriers” combined with Boolean operators. Inclusion criteria comprised studies addressing molecular and cellular mechanisms of chemoresistance such as genetic and epigenetic alterations, CSCs, EMT, and tumor microenvironment influences as well as novel therapeutic strategies including targeted therapy, immunotherapy, and nanotechnology-based approaches. Original research articles, clinical studies, systematic reviews, and meta-analyses were prioritized, while non-English publications, case reports, and irrelevant studies were excluded. As this is not a systematic review, data extracted from eligible studies were qualitatively synthesized to highlight key mechanisms and therapeutic innovations in OSCC drug resistance.

MECHANISMS OF CHEMORESISTANCE IN ORAL CANCER

Genetic Alterations

Tumour Suppressor Gene Mutations (e.g., p53)

Mutations in tumour suppressor genes like p53 have a major impact on the development and spread of cancer, especially oral cancer (Figure 1). Often referred to as the "guardian of the genome," p53 is essential for regulating DNA repair, cell cycle arrest, and apoptosis in response to cellular stress or damage. Comprising 393 amino acids, p53 is a phosphoprotein that is found in the cell nucleus. It was initially identified as a protein that could attach to the big "T"antigen (or protein) that the *Simian virus 40* encodes and that causes cell transformation (Ni *et al*., 2024; Canella *et al*., 2024). Mutations in p53 disrupt these protective functions, allowing damaged cells to proliferate uncontrollably, leading to tumorigenesis. Loss of p53 function in oral cancer is frequently associated with increased resistance to chemotherapy because it impedes the cell's ability to undergo apoptosis in response to treatment.

Oncogene overexpression (e.g., EGFR, Ras)

Oncogene overexpression, such as in EGFR and Ras, is a critical factor in cancer development, including oral cancer. EGFR (Epidermal Growth Factor Receptor) and Ras are key drivers of cell proliferation and survival pathways. They promote unchecked cell proliferation and resistance to apoptosis by continuously activating signalling cascades like the PI3K/AKT and MAPK pathways when they are overexpressed or mutant. The ligand-activated wild type version of EGFR is mimicked by oncogenic mutant forms of the protein. Tumor-derived EGFRs are enzymatically active and transform, but their tyrosine phosphorylation state is significantly lower than that of ligand-activated wild type receptors (Sheng *et al*., 2023). It appears that intracellular signals produced by this very low but persistent activity are distinct from those produced by the conventional biochemical machinery. Receptor endocytosis and degradation

are examples of negative regulation (desensitization) that EGFR mutants commonly avoid, allowing receptor attenuating processes to operate "under the radar" of the modified receptors (Banushi *et al.*, 2023). In oral cancer, the overactivation of these oncogenes contributes to tumor progression and is often linked to chemoresistance, as cancer cells become less responsive to therapy-induced cell death.

DNA Repair Mechanisms And Resistance

By repairing DNA damage brought on by different stressors, such radiation or chemotherapy, DNA repair systems are essential for preserving genomic integrity (Figure 2). Base alterations like 8-deoxyguanosine (Yousefzadeh *et al.*, 2021), abasic sites, bulky adducts, inter- and intra-strand linkages, and single- and double-strand brakes are examples of DNA damage. Numerous proteins are involved in various repair pathways because DNA damage can take many distinct forms. DNA Damage Response (DDR) is the collective term for the activation of several repair processes with the primary objective of restoring DNA integrity. Historically, Fanconi's Anaemia (FA), a rare hereditary condition marked by bone marrow failure, skeletal deformity, and an elevated incidence of malignancy, was linked to these proteins/genes. Genes in the FA pathway, which are essential genes involved in DNA damage repair (Ishiai *et al.*, 2021), are mutated in this uncommon condition. In cancer, defects or alterations in these mechanisms can lead to mutations that drive tumor growth. However, some cancer cells develop enhanced DNA repair capabilities, allowing them to survive and resist the effects of DNA-damaging treatments like chemotherapy. One of the characteristics of cancer is genomic instability and mutations, which will develop if DNA damage is not repaired or is repaired incorrectly (Hanahan *et al.*, 2022). Both the development of cancer and its therapy are impacted by the DDR. Cells that lack DDR are more vulnerable to chemicals that damage DNA, and these defects are referred to as cancer drivers (Barnieh *et al.*, 2021). This increased repair capacity contributes to treatment resistance, as cancer cells can efficiently repair the damage and continue proliferating despite therapeutic intervention.

DRUG EFFLUX AND INACTIVATION

ATP-Binding Cassette (ABC) Transporter Overexpression (e.g., P-glycoprotein)

The increase of ATP-Binding Cassette (ABC) transporters, including P-glycoprotein (P-gp), is a significant determinant in cancer chemoresistance. When Chinese hamster ovary cells showed pleiotropic cross-resistance to a range of amphiphilic medicines in 1976, P-glycoprotein, sometimes referred to as ABCB1 or MDR1, was identified as the first mammalian ABC multidrug transporter (Shchulkin *et al.*, 2021). This transporter, also referred to as ABCB1 or MDR1, was given the name P-gp. By lowering intracellular drug concentrations and decreasing their efficacy, these transporters aggressively pump chemotherapy medications out of cancer cells. According to the pattern of P-gp expression, P-gp's main function is to shield the body from dangerous substances and xenobiotics by removing them into the bile, urine, and faeces and keeping them out of the brain, testes, and foetus (Deeley *et al.*, 2024; Tian *et al.*, 2023). The luminal surface of capillary endothelial cells in the brain and testes, the apical surface of the epithelial cells of the kidneys' proximal tubules, the canalicular surface of hepatocytes in the liver, the columnar epithelial cells of the intestine, and the placenta all express P-gp to achieve this. In addition to its physiological importance, P-gp presents a substantial pharmacological barrier that prevents several clinically used drugs, such as immunosuppressive drugs, cardiac glycosides, cholesterol-lowering statins, antibiotics, calcium channel blockers, HIV protease inhibitors, anti-cancer medications, anti-epileptic medications, and anti-histamines, from reaching their targeted targets (Sajid *et al.*, 2023). Studies on knockout mice have shown that P-gp is crucial in defining the drug's ADME (Absorption, Distribution, Metabolism, and Excretion) profile (Patel *et al.*, 2022; Sajid *et al.*, 2023). These P-gp knock-out mice had reduced drug excretion and increased drug absorption, which led to severe toxicity. Additionally, P-gp and the principal phase I drug metabolizing enzyme P450 (CYP3A4) work together to decrease the oral medication's bioavailability due to their strikingly similar substrates and regulatory mechanisms. Numerous solid tumour malignancies, including kidney, colon, liver, ovarian, breast, and sarcomas (Park *et al.*, 2023), have been found to display high levels of P-gp. Because of inadequate drug accumulation caused by increased P-gp in oral cancer, tumour cells are able to persist and grow in spite of treatment. One of the biggest barriers to successful therapy is ABC transporter-mediated medication efflux.

Role of Multidrug Resistance (MDR) Proteins In Drug Expulsion

Metastases are also linked to chemoresistance, and MDR often follows prolonged chemotherapy, leading to refractory disease and tumour recurrence (Zheng *et al.*, 2017). The fact that acquired MDR cancer cells frequently develop cross-resistance to structurally unrelated chemotherapeutic medicines is another crucial factor to consider (Figure 3). Theoretically, MDR can result from several cellular and non-cellular pathways, including elevated levels of xenobiotic metabolism enzymes (like glutathione-S-transferase), decreased absorption of water-soluble drugs, various cell changes that affect cytotoxic medications' ability to kill cells and enhanced energy-dependent efflux that eliminates hydrophobic pharmaceuticals from cells (Amawi *et al.*, 2019). ABC transporters are a superfamily of membrane proteins that mediate MDR processes in a range of cancer types because they may transfer hydrophobic drugs and lipids from the inner to the outside leaflet of the cell membrane (Catalano *et al.*, 2022). P-gp (MDR1, ABCB1) and MRP are two ABC transporters associated with MDR that may be overexpressed in cancerous

cells. The intracellular medication levels necessary for a successful treatment are deficient as a result of their activity (Dong *et al.*, 2020). Because the medications are effectively eliminated before they may cause cell death, the overexpression of MDR proteins in oral cancer and other malignancies enables cancer cells to survive and grow despite treatment.

AVOIDANCE OF APOPTOSIS

Apoptotic Pathway Dysregulation (Bcl-2, Bax, caspases)

Chemoresistance and cancer progression are significantly influenced by dysregulation of apoptotic pathways, which involve proteins such as caspases, Bax, and Bcl-2. It is well known that maintaining the balance between cell survival and apoptosis depends on the BCL-2 protein family. BCL-2 primarily improves lifespan by blocking the release of apoptogenic proteins such cytochrome c from the mitochondria by binding to the pro-apoptotic proteins BCL2-associated-X-protein (BAX) and BCL-2 homologous antagonist killer (BAK) (Glover *et al.*, 2024). A variety of haematopoietic lineage cells and many neoplastic types express BCL-2, which was initially identified as a potential oncogene in acute B cell leukaemia (Garimberti *et al.*, 2024, Alam *et al.*, 2022). Myeloid Cell Leukaemia sequence-1 (MCL1), BCL-2-like-2 (BCL-W), BCL-2-related protein A1A (BCL-A1A), and B-cell lymphoma extra-large (BCL-XL) are the other four members of the pro-survival family in addition to BCL-2 (Qian *et al.*, 2022). An imbalance between these proteins, with increased Bcl-2 and decreased Bax expression, inhibits apoptosis, allowing cancer cells to evade death. Further hindering the cell's capacity to undergo programmed death is the dysregulation of caspases, the enzymes that carry out apoptosis (Figure 4). During chemotherapy, this resistance to apoptosis helps cancer cells survive.

Autophagy As A Survival Mechanism In Cancer Cells

Autophagy is essential for maintaining cellular homeostasis and breaking down ageing proteins and damaged organelles (Figure 5) (Santana-Codina *et al.*, 2017; Sanchez-Garrido *et al.*, 2021; Kuo *et al.*, 2018). Autophagy has two functions in cancer biology: it promotes and suppresses tumours and aids in the growth and multiplication of cancer cells (Duan *et al.*, 2022; Cong *et al.*, 2022). Autophagy can be controlled by certain anticancer medications. As a result, autophagy-regulated chemotherapy may affect whether cancer cells survive or die (Debnath *et al.*, 2023; Das *et al.*, 2018). Furthermore, the expression of oncogenes or tumour suppressor proteins is influenced by autophagy control. Tumour suppressor factors are adversely regulated by mTOR and AMPK, which induces autophagy and suppresses the beginning of cancer (Giorgi *et al.*, 2016). However, oncogenes can be activated by mTOR, class I PI3K, and AKT, which inhibits autophagy and encourages the growth of cancer (Deretic *et al.*, 2018). Reduced and abnormal autophagy, which stops oxidatively challenged cells from breaking down damaged proteins or components, leads to the development of cancer. Moreover, basal autophagy is believed to have a role in cancer suppression (Wang *et al.*, 2018; Wijishake *et al.*, 2021). It is possible to modify key autophagy proteins to prevent cancer growth.

CANCER STEM CELLS (CSCS) AND TUMOR HETEROGENEITY

Chemoresistance and Tumour Recurrence: The Function of CSCs

Chemoresistance and tumour recurrence are significantly influenced by Cancer Stem Cells (CSCs). Because these cells can self-renew and differentiate into different cell types, they can rebuild the tumour after the initial therapy. CSCs are often resistant to chemotherapy due to several factors, including efficient DNA repair mechanisms, increased drug efflux capacity via transporters, and the activation of survival pathways. Cells that have evaded chemotherapy are frequently blamed for primary and metastatic sites of recurrence after chemotherapy. Researchers have examined chemoresistance as a functional mechanism for identifying and isolating CSCs because it has been suggested that these cells are the primary tumor-initiating cells during recurrence. One such method that has shown promise in several cancer types is the identification of CSCs by enhanced efflux of Hoechst 33342 dye through ATP-Binding Cassette (ABC) transporters. They are known as Side Population (SP) cells in flow cytometry investigations and were initially demonstrated to be useful in hematopoetic stem cell separation (Che *et al.*, 2022). One of the earliest studies employing SP analysis as a method for CSC enrichment used the C6 rat glioma cell line (Pournajaf *et al.*, 2024). In this study, SP cells were identified as the main tumor-initiating CSCs for the C6 cell line. Additionally, SP cells possess self-renewal and differentiation traits that set CSCs apart, as seen by their capacity to repopulate both SP and non-SP cells. Since this study, CSCs have been found in a wide range of solid tumours, such as ovarian, colon, liver, and breast malignancies, using SP analysis (Saha *et al.*, 2021; Kai *et al.*, 2024; Hayakawa *et al.*, 2021; Lv *et al.*, 2021). Their inherent resistance allows them to survive chemotherapy, leading to tumor regrowth and recurrence. Targeting CSCs is crucial for overcoming chemoresistance and preventing tumor relapses.

Tumor Microenvironment And Heterogeneity Contributing To Resistance

The Tumor Microenvironment (TME) and its heterogeneity significantly contribute to cancer resistance. Numerous non-cancerous cells, including blood vessels, fibroblasts, and immune cells, make up the TME. These cells interact with cancer cells to promote their development and survival. This complex environment promotes resistance by secreting growth factors, modifying immune responses, and creating physical barriers

to drug delivery. Additionally, tumor heterogeneity variations in genetic and phenotypic profiles within the tumor enables subpopulations of cancer cells to adapt and resist therapy. These factors make tumors more resilient to treatment and drive recurrence (Hass *et al*., 2020).

EPITHELIAL-MESENCHYMAL TRANSITION (EMT)

Mechanisms Of EMT And Its Link To Drug Resistance

EMT is the process by which epithelial cells change into invasive mesenchymal cells and lose their apical-basal polarity and cell-cell adhesion (Figure 6). The process by which cells transform from motile, multipolar mesenchymal types to polarised epithelial types is called the Mesenchymal-Epithelial Transition (MET), which is the reverse of EMT. Numerous physiological and pathological processes, including chemotherapy resistance, wound healing, cancer cell metastasis, and embryonic development, are impacted by EMT (Dvoryashina *et al*., 2021; Manfioleti *et al*., 2022; Nieto *et al*., 2016). Numerous molecular changes in cells are described by EMT. Mesenchymal genes, such as vimentin, fibronectin, and N-cadherin, are expressed more frequently in EMT-undergoing cells than epithelial genes, such as occludin, ZO-1, and E-cadherin. E-cadherin depletion is typically a sign of EMT alterations in gene expression during EMT, resulting in a variety of phenotypic alterations, including changed cell shape, a loss of adhesion, and the appearance of stem cell-like features (Huang *et al*., 2022). By encouraging behavioural changes in cells, such as reduced cell-cell adhesion and enhanced motility, which aid cancer cells in avoiding chemotherapy, EMT contributes to drug resistance in cancer. EMT-associated transcription factors also activate survival pathways and drug efflux pumps, reducing drug sensitivity. This transition makes cancer cells more resilient to therapy, enabling them to survive and contribute to metastasis and tumor recurrence.

EMT As A Pathway For Metastasis And Therapy Evasion

One important mechanism that promotes metastasis and therapy evasion in cancer is the Epithelial-to-Mesenchymal Transition (EMT). At several phases of development, morphological alterations seen during EMT are identified. Cancer cells acquire mesenchymal traits like increased motility and invasiveness during EMT while losing epithelial traits like strong cell adhesion. As a result, they can separate from the main tumour, infiltrate nearby tissues, and travel to other organs. EMT also helps cancer cells evade therapy by making them more resistant to apoptosis and increasing their survival mechanisms. The tumor-associated stroma controls the invasive behaviour of tumour epithelia (Sharma *et al*., 2022). One challenge in the clinical management of cancer is the ongoing buildup of these cells throughout the recurrent phase after therapy. Tumour fibroblasts have long been implicated in therapeutic resistance, according to research findings. In this regard, EMT plays a part in reducing the efficacy of treatment for various tumours, including those of the pancreas and prostate (Gao *et al*., 2024; Palamaris *et al*., 2021; Hu *et al*., 2021). Consequently, EMT enables both metastasis and resistance to treatments, contributing to cancer progression and relapse.

TUMOR MICROENVIRONMENT (TME) AND HYPOXIA

Role Of Hypoxia-Induced Factors (HIF-1α) In Drug Resistance

In both local and remote OTS contexts, hypoxia seems to be beneficial. As was previously established, osteosarcoma cells usually develop in the local environment of growth plates, which is favourable to changes in oxygen levels. Changes in the hypoxia biomarkers seem to be associated with the development and course of osteosarcoma. Numerous studies have linked the poor prognosis of OTS to specific biomarkers, such as mTOR, HIFs, or CA IX (Carbonic Anhydrase IX) (Li *et al*., 2016; Zhang *et al*., 2018). They highlight how OTS cancer development, treatment resistance, and metastatic tendency are all primarily caused by hypoxia. An analysis of the study materials might be used to demonstrate the idea of hypoxia in osteosarcomas using tumour collections and *in vitro* or *in vivo* preclinical models. However, HIF-1α, which is frequently overexpressed in both locally aggressive and metastatic OTS, is the main hypoxia-related marker linked to OTS (Schito *et al*., 2016). Overexpression of GLUT-1 (Glucose Transporter 1), CA IX, or VEGF/VEGFR can account for the overall improvement of hypoxic pathways from the membrane to the nucleus and the rise in intra-tumor microvessel density (Dzhalilova *et al*., 2021; Okuno *et al*., 2018; Ma *et al*., 2022; Capasso *et al*., 2019). HIF-1α was widely acknowledged at that time as a key component in changing the tumour microenvironment. HIF-2α appears to be involved in apoptosis and the promotion of OTS stemness features, however it has not been investigated as much as its homologues (Wang *et al*., 2017; Zhao *et al*., 2019; Irelli *et al*., 2019). Consequently, HIF-2α was found to be a key driver in OTS cells that underwent a specific metabolic alteration (Todd *et al*., 2020). mTOR integrated the effects of OTS cells and the cancer microenvironment, which were typically closely connected to autophagic processes and Pi3K/AKT upstream signalling triggered by different tyrosine kinase receptors (Todd *et al*., 2020; Niu *et al*., 2019; Feng *et al*., 2016). For example, because hypoxia is present from the beginning of OTS cells, it is still unclear how precisely all those signs interact throughout OTS progression and metastatic propension. More recently, research has linked extensive intra-tumor hypoxia to enhanced genomic instability in cancer cells, especially osteosarcomas, which often exhibit high levels of chromothripsis and chromosomal breakage (Smida *et al*., 2017). These tumour forms usually exhibit significant levels of microRNA dysregulation during hypoxia, which is associated with genomic instability and complexity as well as poor prognosis.

Chromosome imbalance and the development of osteosarcoma in OTS have likely been linked to miRNA-133a (Yang *et al.*, 2020).

Influence Of Immune Cells, Fibroblasts, And Extracellular Matrix (ECM) On Chemoresistance

T-regulatory cells (Tregs), Myeloid-Derived Suppressor Cells (MDSCs), and Tumor-Associated Macrophages (TAMs) collaborate to produce an immunosuppressive Tumour Microenvironment (TME) that encourages cancer survival and spread. TAMs release cytokines such TGF-β and IL-10, which stimulate the growth of tumours, decrease T cell activity, and encourage the proliferation of Treg cells. Tregs obstruct anti-tumor immune responses by ingesting IL-2, secreting immunosuppressive cytokines, and blocking effector T cells with molecules such CTLA-4. MDSCs further hinder T cell activity by producing reactive oxygen species, using fewer vital resources, and upregulating immunological checkpoints such PD-L1. When combined, these cells help malignancies evade the immune system, lower the immunological response, and become more resistant to immunotherapy and chemotherapy. Cancer-Associated Fibroblasts (CAFs) have several protumorigenic roles in the tumour microenvironment (Renner *et al.*, 2017). These preclinical discoveries suggest that CAFs may be reduced, eliminated, or reprogrammed, however clinical translation of these findings has not yet occurred. Without a doubt, a better understanding of these cells and their functions will improve cancer treatments. Fibroblasts, which are found in almost all organs and healthy tissues, promote inflammation and fibrosis, which helps wounds heal. Activated fibroblasts of the mesenchymal lineage that promote fibrosis and inflammation around tumours are known as cancer-associated CAFs. CAFs are characterised by their morphology and association with cancer cells, as well as the lack of lineage markers for haematopoietic, endothelial, and epithelial cells (Sahai *et al.*, 2020; Biffi *et al.*, 2020). The Extracellular Matrix (ECM) provides structural support and biochemical signals to osteosarcoma cells, facilitating their motility, invasion, and dissemination. Remodelling enzymes such Matrix Metalloproteinases (MMPs) break down the Extracellular Matrix (ECM) in osteosarcoma, changing its composition and enabling the growth of cancer cells. Additionally, through interactions with integrins and other cell surface receptors, the Extracellular Matrix (ECM) activates signalling pathways that improve cell invasion, motility, and survival. Additionally, to facilitate metastasis to distant organs including the lungs and promote cancer cell penetration into adjacent tissues, the Extracellular Matrix (ECM) hardens and reorganizes. These ECM changes impact osteosarcoma's aggressiveness and resistance to treatment (Cui *et al.*, 2020). The major mechanisms contributing to drug resistance in OSCC are summarized in Table 1.

RESULTS

This review highlights multiple contributors to drug resistance in OSCC, including activation of PI3K/Akt, NF-κB, and Wnt/β-catenin pathways, overexpression of efflux transporters, EMT, and CSCs. The tumor microenvironment, particularly hypoxia and cancer-associated fibroblasts, plays a key role via metabolic and signaling changes. Epigenetic alterations

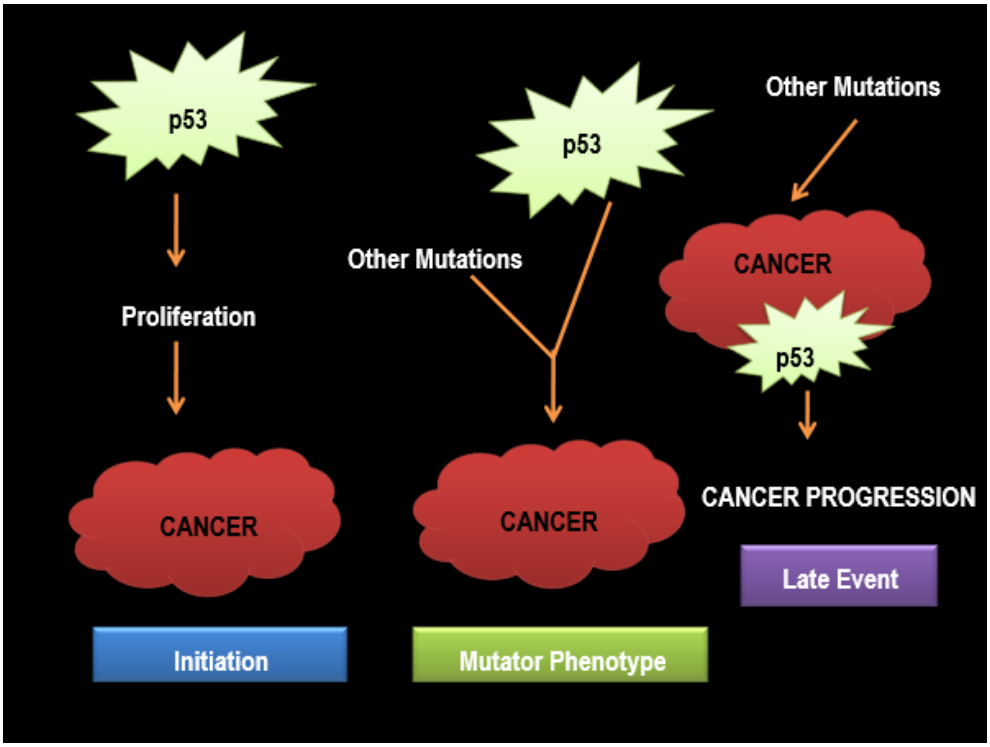

Figure 1: Mutations in Tumor Suppressor Genes (e.g., p53).

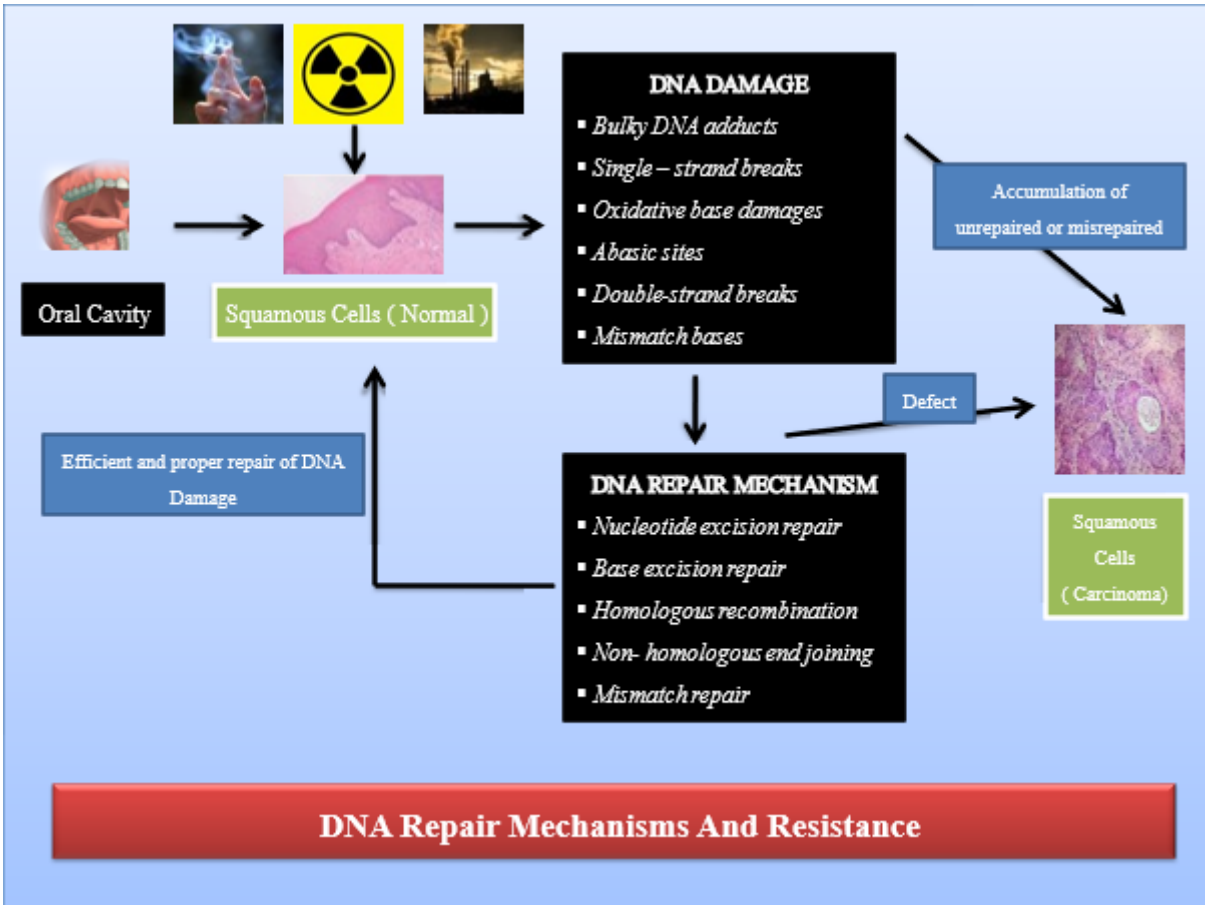

Figure 2: DNA Repair Mechanisms and Resistance.

further regulate chemoresistance. Emerging strategies such as nanotechnology, RNA therapeutics, CRISPR-Cas9, and immunotherapies like checkpoint inhibitors and CAR-T cells show promise. Combination therapies targeting both molecular and environmental mechanisms offer improved treatment efficacy, underscoring the need for a multi-targeted approach in OSCC management.

STRATEGIES TO OVERCOME CHEMORESISTANCE IN ORAL CANCER

Targeted Therapies

EGFR Inhibitors (e.g., cetuximab)

Targeted therapies for cancer, particularly colorectal and head and neck tumours, include cetuximab and other EGFR (Epidermal Growth Factor Receptor) inhibitors. These inhibitors block the EGFR pathway, which is often overexpressed or mutated in various cancers, leading to uncontrolled cell growth and proliferation. The US Food and Drug Administration has approved cetuximab, a chimeric IgG1 monoclonal antibody against EGFR, as a therapy for LA and RM SCCHN. Numerous potential anti-tumor mechanisms could be responsible for the encouraging outcomes of cetuximab therapy in SCCHN. As a competitive ligand, cetuximab binds to the EGFR's extracellular domain more strongly than its native ligand, blocking further contact (Nair *et al.*, 2022; Li *et al.*, 2023). Cetuximab inhibits EGFR expression by internalising and degrading the receptor in addition to directly blocking EGFR, which stops additional downstream cascade signaling (Vigneswara *et al.*, 2018; Taberna *et al.*, 2019). Finally, the IgG1 backbone of cetuximab can attach to Natural Killer cells (NK cells) and trigger Antibody-Dependent Cellular Cytotoxicity (ADCC), which allows immune cells to target and eliminate particular cells (Taberna *et al.*, 2019; Campbell *et al.*, 2016; Baysal *et al.*, 2020). To increase the effectiveness of treatment, cetuximab is frequently administered in conjunction with radiation therapy or chemotherapy. Long-term efficacy is frequently limited by the development of EGFR inhibitor resistance.

Targeting Molecular Pathways to Overcome Resistance (e.g., PI3K/AKT/mTOR, MAPK)

By blocking biochemical pathways including PI3K/AKT/mTOR and MAPK, EGFR inhibitors and other cancer medicines can overcome resistance. The PI3K/AKT/mTOR pathway, which is frequently activated in cancers, supports cell survival, proliferation, and metabolism. When EGFR is inhibited, cancer cells can bypass this blockade by activating PI3K/AKT/mTOR signaling, contributing to resistance. Similarly, the MAPK (RAS/RAF/MEK/ERK) pathway, which regulates cell growth and differentiation,

can also be upregulated, allowing tumors to continue growing despite EGFR inhibition. The AKT/mTOR pathway is crucial for cancer cells' ability to withstand chemotherapy and radiation, according to a growing body of research. Because blocking this route may help reverse chemoresistance and radio resistance, it is a desirable target for the development of cancer treatments against OSCC. Chemosensitization caused by mixing chemotherapy medications with other medications has been linked to this route. By blocking the AKT/mTOR pathway and other related pathways, pantoprazole treatment, for example, has been shown to chemosensitize chemoresistant oral epidermoid carcinoma cells to vincristine both *in vitro* and *in vivo* (Lu *et al.*, 2019; Dai *et al.*, 2017). Similarly, it has been shown that by deactivating proteins like mTOR, AKT, and eukaryotic translation Initiation Factor (eIF4E) 4E (4E-BP1), the antiviral drug ribavirin chemosensitizes OSCC cells to paclitaxel. Acetylshikonin dramatically reduced the growth of cisplatin-resistant OC in both *in vitro* cellular models and *in vivo* xenograft animal models by disrupting the mTOR/PI3K/AKT signalling pathway (Shao *et al.*, 2025). Another preclinical study demonstrated the potent anticancer impact of cetuximab, an anti-EGFR medication, in combination with temsirolimus, a mTOR inhibitor, using an orthotopic model of HNSCC. The synergistic effect of this drug combination has also been shown to be mediated by the inhibition of the PI3K/mTOR pathway (Yasothkumar *et al.*, 2025). Using inhibitors to target these pathways (e.g., PI3K inhibitors, mTOR inhibitors, or MEK inhibitors) can help block these compensatory survival signals and restore sensitivity to EGFR inhibitors, making combination therapies a promising approach to combat chemoresistance. Table 2 summarizes key molecular targets and inhibitors investigated for oral cancer therapy.

Approaches to Eliminate Cancer Stem Cells (e.g., ALDH inhibitors)

Targeting Cancer Stem Cells (CSCs) is crucial for overcoming tumor recurrence and therapy resistance, as these cells have self-renewal capabilities and drive cancer progression. According to reports, CD44+ cells in Head and Neck Squamous Carcinoma (HNSCC) have the special characteristics of CSCs (Singh *et al.*, 2021). Furthermore, compared to CD24−CD44+ cancer cells, CD24+CD44+ cells were found to be more tumorigenic and chemoresistant (Elkashyty *et al.*, 2020). In HNSCC, CD133 has also been studied as a CSC marker; in line with this, CD133+ cells displayed decreased paclitaxel sensitivity (Ma *et al.*, 2020; Reid *et al.*, 2017). In a different study, CD10+ HNSCC cells displayed OCT3/4, had aggressive tumorigenic and sphere-forming characteristics, and were comparatively resistant to radiation and cisplatin (Han *et al.*, 2014), indicating that CD10 might be a hallmark of HNSCC CSCs. NANOG, OCT4, and SOX2 expression levels were strongly connected with EMT-associated markers and a poorer prognosis in nasopharyngeal cancer (Balbinot *et al.*, 2023). In a mouse model of oral squamous carcinoma, Lin28, an essential element for cellular reprogramming and the generation of induced pluripotent stem cells, was found to improve stemness

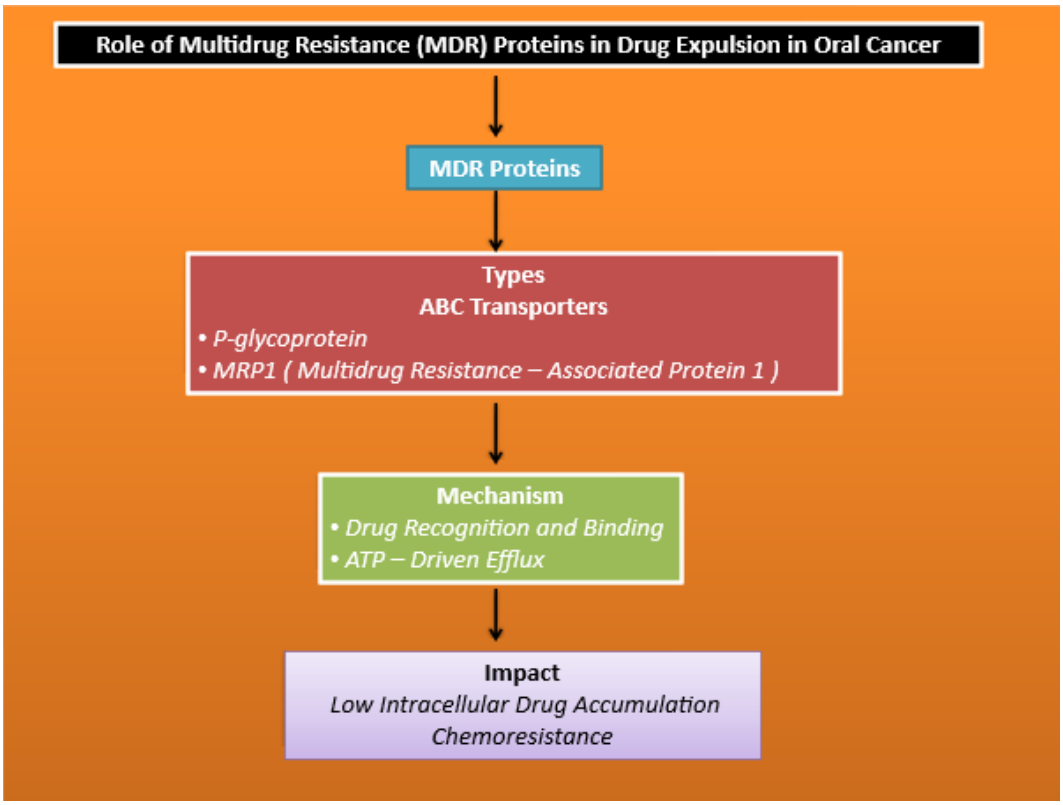

Figure 3: Role of Multidrug Resistance (MDR) Proteins in Drug Expulsion.

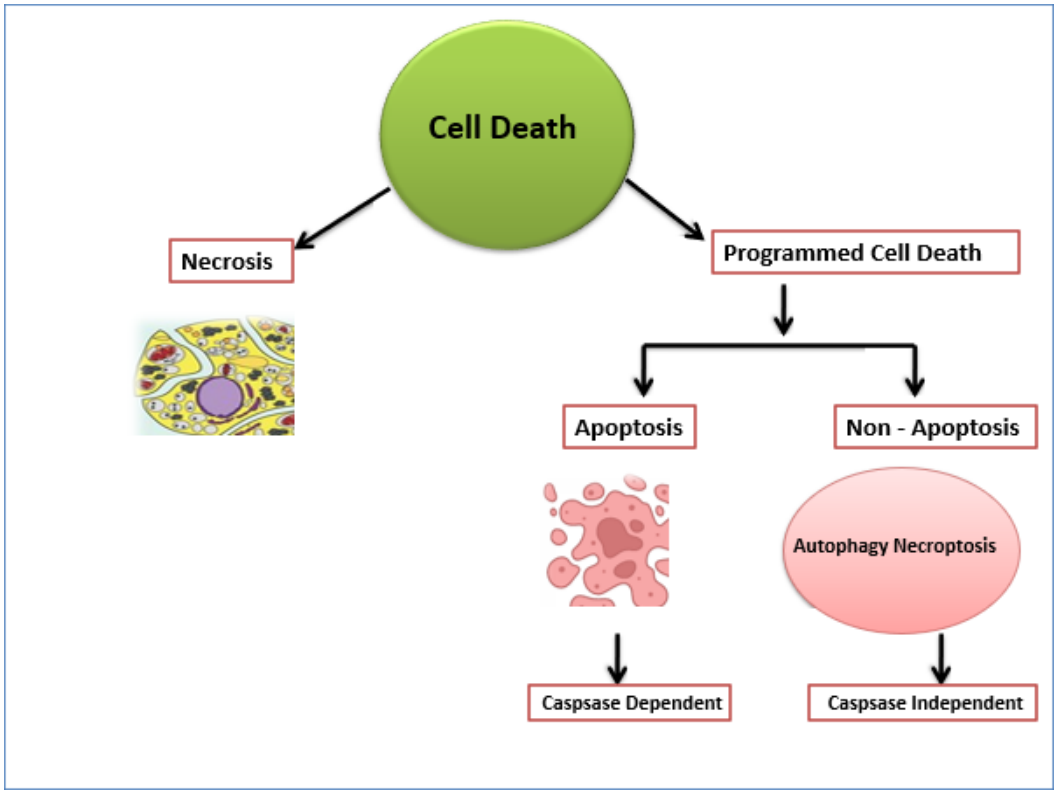

Figure 4: General Mode of Cancer Cell Death.

traits by blocking Let-7 and stimulating Oct4 and Sox2 (Chen *et al.*, 2019). Increased ALDH1 activity promotes carcinogenesis and lessens the impact of chemoradiotherapy since ALDH1 has also been thought to be a CSC marker in HNSCC (Singh *et al.*, 2021). Furthermore, compared to cells expressing CD44+ alone, ALDH+CD44+ HNSCC cells exhibit higher stemness properties and are more tumorigenic (Reid *et al.*, 2017). By disrupting these pathways and features, these strategies aim to eradicate CSCs and reduce the risk of cancer relapse and metastasis.

COMBINATION THERAPIES

Integrating Chemotherapy with Radiotherapy or Immunotherapy

Combining chemotherapeutic agents with radiotherapy or immunotherapy in oral cancer has shown promising results in improving treatment outcomes**.** Chemotherapy, using agents like cisplatin or 5-fluorouracil, works by damaging DNA or disrupting cell division, making cancer cells more sensitive to radiation (chemoradiotherapy). This combination enhances the cytotoxic effect on tumor cells, particularly in locally advanced stages, while helping to shrink tumors for better surgical outcomes. However, this approach often leads to significant side effects, including mucositis and dysphagia. Immunotherapy, such as immune checkpoint inhibitors, is used in conjunction with chemotherapy to target and eradicate cancer cells (like pembrolizumab or nivolumab). Immunotherapy can boost the immune response against oral cancer, and when paired with chemotherapy, it may reduce tumor size while helping to overcome immune evasion mechanisms. This dual strategy is presently being investigated in a number of clinical trials and may be more successful, especially in cases of recurrent or metastatic oral cancer. The combination of these therapies aims to increase survival rates while targeting different aspects of tumor biology, though the risk of toxicity and patient tolerance remains a challenge (Krishnan *et al.*, 2024).

Enhancing Efficacy by Combining Conventional Drugs with Novel Inhibitors

Combining traditional chemotherapy drugs with novel inhibitors often leads to synergistic effects, enhancing treatment efficacy beyond what either approach achieves alone. Traditional chemotherapeutic agents, such as platinum-based drugs or taxanes, target rapidly dividing cancer cells by causing DNA damage or disrupting microtubule formation. However, tumors often develop resistance to these agents through activation of alternative survival pathways or cancer stem cells. Novel inhibitors, like Tyrosine Kinase Inhibitors (TKIs), PI3K/AKT/mTOR inhibitors, or immune checkpoint inhibitors, aim to target particular molecular pathways that support tumour survival, growth, and resistance. When combined with traditional drugs, these novel agents can block compensatory mechanisms, reduce drug resistance, and sensitize cancer cells to chemotherapy. For example, combining cisplatin with EGFR inhibitors (like cetuximab) in head and neck cancers can increase tumor cell death by disrupting both DNA repair and growth signaling pathways. Stathmin expression and phosphorylation are regulated by the

PI3K/AKT/mTOR pathway, which has been shown to be active in OSCC patients. Therefore, by decreasing stathmin expression and phosphorylation, increasing apoptosis, and delaying tumour growth, PI3K inhibition causes OSCC cells to become resensitised to the TPF therapy (Ju *et al.*, 2020). Combining Cisplatin with PI3K/AKT/mTOR pathway inhibitors was considered possible in clinical studies; one research demonstrated encouraging OS and Progression-Free Survival (PFS) rates (Gulati *et al.*, 2020; Day *et al.*, 2020). Similarly, using PI3K/AKT/mTOR inhibitors alongside chemotherapy may prevent resistance by blocking survival pathways, while immune checkpoint inhibitors can enhance the immune response to tumors already damaged by chemotherapy. This synergistic combination not only improves overall treatment response but can also lower the required dose of each drug, potentially reducing toxicity and side effects.

BLOCKING DRUG EFFLUX MECHANISMS

ABC Transporter Inhibitors

Compounds known as ABC transporter inhibitors prevent ATP-Binding Cassette (ABC) transporters from acting, which is essential for (MDR) in cancer. Membrane-bound proteins known as ABC transporters, such as (ABCB1), (MRP1), and (BCRP), aggressively pump chemotherapeutic medicines out of cancer cells, decreasing drug accumulation and efficacy. This leads to chemotherapy resistance, particularly in aggressive or recurrent cancers. By increasing the efflux of substrate TKIs, MDR-associated ABC transporters produce TKI resistance. Several investigations have shown that certain TKIs may block these transporters and decrease their drug efflux activity at clinically realistic dosages, reversing MDR to traditional chemotherapeutic medicines in cancer cells (Kawecki *et al.*, 2019; Patel *et al.*, 2022; Ramaiah *et al.*, 2021). One possible therapy strategy for drug-resistant malignancies is the use of TKIs to lower ABC drug transporter mediated-MDR in patients. By obstructing RTK's ATP-binding pocket and halting the phosphorylation pathway that follows, a TKI prevents cell survival and proliferation. However, some TKIs that both bind to the transporter's substrate-binding pocket and are released by the energy-dependent hydrolysis of ATP molecules lower the intracellular TKI concentration. Some examples of ABC transporter inhibitors include, Verapamil, Elacridar and Tariquidar. Despite their potential, many ABC transporter inhibitors have faced challenges in clinical translation due to toxicity, poor selectivity, or pharmacokinetic interactions with other drugs. Nevertheless, ongoing research continues to explore more effective and less toxic inhibitors to overcome MDR and improve cancer treatment outcomes.

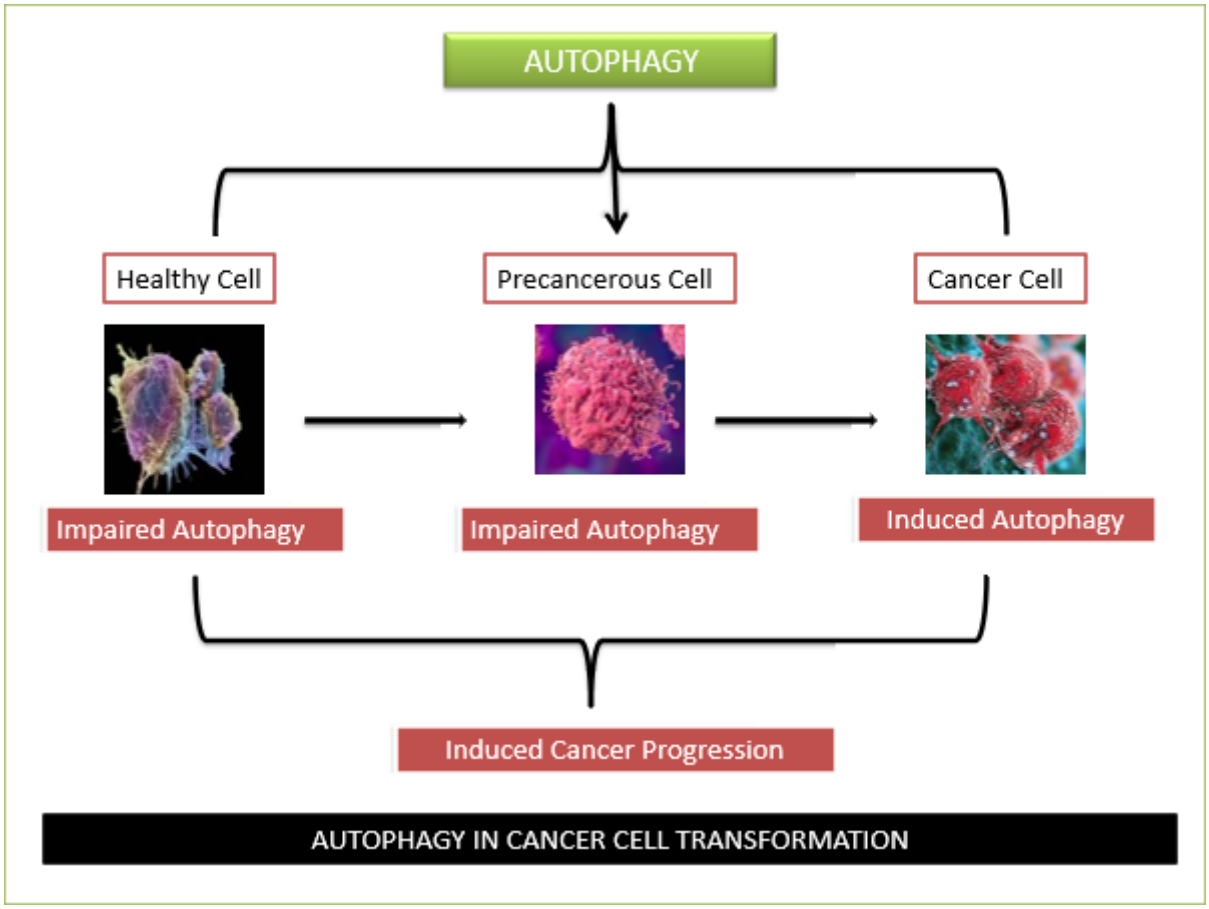

Figure 5: Autophagy in Cancer Cell Transformation.

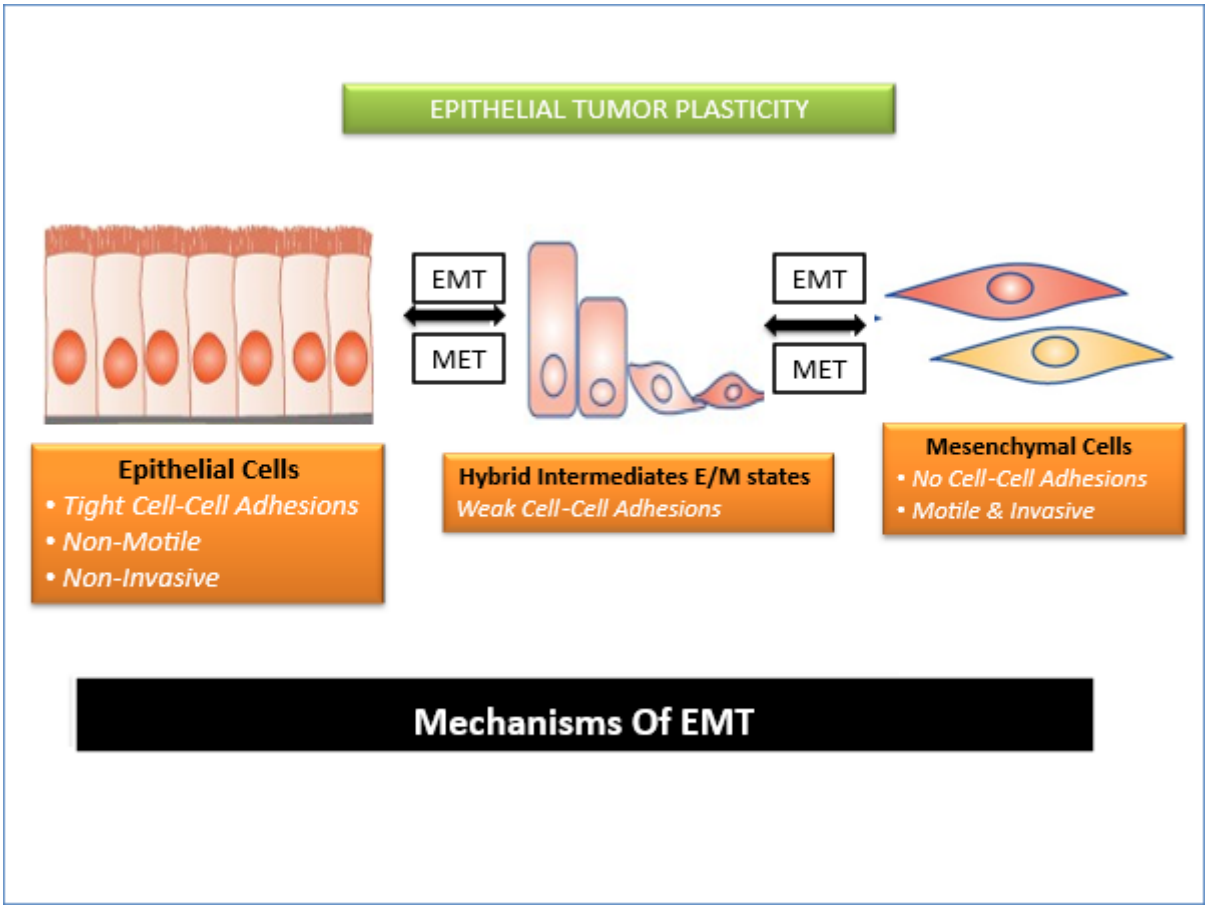

Figure 6: Mechanism of Epithelial-Mesenchymal Transition (EMT).

Utilizing Small Molecules to Inhibit MDR Proteins

P-glycoprotein, MRP1, and BCRP are examples of Multidrug Resistance (MDR) proteins that actively pump chemotherapeutic medicines out of cancer cells. These proteins are blocked by small chemicals, leading to treatment failure. These inhibitors, like tariquidar (P-glycoprotein), probenecid (MRP1), and ko143 (BCRP), work by binding to the MDR transporters and preventing drug efflux, thereby increasing the intracellular concentration of chemotherapeutic agents. By overcoming drug resistance, these small molecule inhibitors enhance the effectiveness of chemotherapy. However, challenges like toxicity and poor selectivity remain, prompting ongoing research to develop safer and more effective inhibitors (Dallavalle *et al.*, 2020).

EPIGENETIC MODULATION

Impact of HDAC Inhibitors and DNA Methyltransferase Inhibitors

Because they reverse aberrant gene silence linked to cancer and other disorders, (HDAC) inhibitors and DNA methyl transferase inhibitors are essential components of epigenetic treatment. By keeping acetyl groups from being removed from histones, HDAC inhibitors increase gene expression by creating a more open chromatin structure. By preventing methyl groups from being added to DNA, especially at CpG islands in gene promoters, DNA methyl transferase inhibitors can restore the expression of tumour suppressor genes, which are commonly repressed in cancer. Different HDAC inhibitors kill cancer cells in several ways, such as by altering histone and non-histone proteins and altering gene expression. The high levels of histone acetylation present in many tumours change the expression of the genes involved in cell signalling. 2%-10% of genes involved in several biological processes, including cell cycle arrest and apoptosis induction, exhibit altered expression when HDACs are repressed (Mehta *et al.*, 2021). It has been shown that HDAC inhibition modifies several genes involved in the regulation of the cell cycle and apoptosis (Chen *et al.*, 2022; Ramaiah *et al.*, 2021). Furthermore, several HDAC inhibitors exhibit antiangiogenic characteristics (Mu *et al.*, 2024). Since both classes of inhibitors aim to reactivate genes necessary for normal cellular function, they may be able to treat cancer and other conditions involving epigenetic dysregulation.

Addressing Epigenetic Changes to Overcome Chemoresistance

One possible method for reversing chemoresistance in cancer treatment is to target epigenetic changes. Chemoresistance is often the result of changes in gene expression caused by epigenetic

changes including DNA methylation, histone modifications, and non-coding RNA control. These changes can decrease the effectiveness of chemotherapy by activating drug-resistant pathways or silencing tumour suppressor genes. Drugs such as DNA methyl transferase inhibitors and Histone Deacetylase (HDAC) inhibitors can remodel the epigenetic landscape. These inhibitors can increase the susceptibility of cancer cells to chemotherapy by re-expressing genes that have been silenced, such as those involved in DNA repair, apoptosis, and cell cycle regulation. This approach helps overcome resistance and increases the long-term effectiveness of cancer treatment (Ponnusamy *et al.*, 2020).

IMMUNOTHERAPY APPROACHES

Role Of Checkpoint Inhibitors (e.g., PD-1/PD-L1 inhibitors)

Because they allow the immune system to recognise and eliminate tumour cells, checkpoint inhibitors such as PD-1/PD-L1 inhibitors are essential for cancer immunotherapy. As a "brake" to prevent autoimmunity, the PD-1 receptor on T cells normally interacts with PD-L1 on cancer cells or other immune cells to lower the immunological response. However, by overexpressing PD-L1, numerous malignancies take advantage of this mechanism, thereby evading immune detection and destruction. When PD-1/PD-L1 drugs prevent this interaction, the immune system's "brake" is released. This makes it possible for T cells to reawaken, identify tumour cells as alien, and launch a potent anti-tumor defence. By increasing the body's immune surveillance and eradicating cancer cells, these inhibitors have demonstrated extraordinary efficacy in treating a variety of malignancies, including melanoma, non-small cell lung cancer, and bladder cancer (Liu *et al.*, 2021).

CAR-T Cell Therapy in Oral Squamous Cell Carcinoma

CAR-T cell therapy is one cutting-edge immunotherapy that has potential for treating oral cancer. Chimeric antigen receptors, or CARs, are created by genetically altering a patient's T cells to specifically target the tumor-associated antigens of cancer cells. Finding the appropriate antigens, such as EGFR, HER2, or MUC1, is necessary to create CAR-T cells that can selectively bind and destroy tumour cells without endangering healthy tissue in cases of oral cancer. Tumor-Associated Antigens (TAAs), which are widely distributed in Oral Squamous Cell Carcinoma (OSCC), are important targets in CAR-T therapy for OSCC. Examples of these antigens that are taken into account for this targeted therapeutic strategy are ErbB and MUC (Tong *et al.*, 2024). These proteins are important possibilities for CAR-T cell targeting because they are frequently overexpressed in cancer cells. OSCC may exhibit overexpression of the ErbB protein family, which is important in cell proliferation and differentiation. Another protein that is frequently detected in greater quantities in a variety of malignancies, including OSCC (Summers *et al.*, 2023), is MUC1. The fact that both antigens are more common in cancer cells than in healthy cells makes them interesting targets for CAR-T therapy. This could enable the modified T-cells to target the antigens more precisely. Other strategies, such as dual-targeting CAR-T cells, combination therapy with immune checkpoint inhibitors, and targeting non-tumor cells of the (TME), such as (Tregs), and (CAFs), are being researched to increase the efficacy and safety of CAR-T cell immunotherapy in OSCC.

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS

Nanoparticles for Precise Drug Delivery and Minimizing Systemic Toxicity

Targeted medication delivery using nanoparticles is a very successful strategy that greatly improves treatment accuracy and lowers systemic toxicity. They can enhance drug accumulation

Table 1: Mechanisms of Drug Resistance in OSCC.

Resistance Mechanism	Key Molecular Players	Effect on Therapy	Representative References
Drug efflux	ABC transporters (MDR1, BCRP, MRP)	Reduced intracellular drug accumulation	Recent OSCC studies
DNA damage repair	FA pathway, DDR proteins, ATM/ATR	Enhanced survival after chemotherapy	Clinical and preclinical reports
Apoptosis evasion	BCL-2 family (BCL-XL, MCL1, BCL-W, BAX, BAK)	Resistance to apoptosis-inducing drugs	Molecular oncology studies
EMT	EMT markers, TGF-β, Wnt signaling	Increased invasion and chemoresistance	OSCC EMT reviews
Cancer stem cells	ALDH, CSC markers, SP cells	Tumor recurrence and multidrug resistance	CSC-focused literature
Hypoxia	HIF-1α, CA IX, GLUT-1	Reduced drug sensitivity	Tumor microenvironment studies

Table 2: Targeted Therapies and Inhibitors Used in Oral Cancer.

Target Pathway	Inhibitor / Drug Class	Mechanism of Action	Clinical Status
EGFR	Cetuximab	EGFR monoclonal antibody	Approved
PI3K/Akt/mTOR	PI3K inhibitors, mTOR inhibitors	Suppress survival signaling	Clinical trials
MAPK	MEK inhibitors	Inhibit proliferation pathways	Investigational
HDAC	HDAC inhibitors	Epigenetic modulation	Preclinical/clinical
VEGF/VEGFR	Bevacizumab, TKIs	Anti-angiogenic	Clinical trials
Immune checkpoints	PD-1/PD-L1 inhibitors	Restore immune response	Approved/clinical

at the tumour site while reducing exposure to healthy tissues by designing nanoparticles to deliver therapeutic compounds directly to sick tissues, such as cancer cells. Nanoparticles can be functionalised with ligands or antibodies that bind to receptors overexpressed on cancer cells in order to guarantee precise distribution. To improve the duration of bloodstream circulation and medication release, their size, shape, and surface characteristics can also be altered. By restricting the drug's influence on non-target tissues, this focused strategy not only increases the medications' effectiveness but also lowers their negative side effects and systemic toxicity. The use of nanoparticles in cancer treatment has shown great promise, as well as in treating other diseases where selective drug delivery is crucial (Deivayanai *et al.*, 2024).

Function of Nanocarriers in Overcoming Resistance Mechanisms

By enhancing medication delivery to resistant tumour cells and removing obstacles that restrict the efficacy of conventional therapies, nanocarriers are essential for avoiding resistance mechanisms in cancer therapy. Chemoresistance-causing mechanisms, such as drug efflux pumps, altered drug metabolism, and modifications to the tumour microenvironment, are frequently developed by cancer cells. Examples of nanocarriers designed to evade these resistance mechanisms include dendrimers, liposomes, and polymeric nanoparticles. According to a study by Chen and colleagues in 2015 (Dang *et al.*, 2024; Patel *et al.*, 2024). One new approach to reducing multidrug resistance is the pooling of siRNAs using nanocarriers. By inhibiting the no flow and efflux-related protein pumps that are linked to or overexpressed in multidrug resistance, this technique improves the efficacy of presently prescribed drugs. In order to increase the therapeutic efficacy against cancer that is resistant to treatment, loading siRNA with cisplatin into Nanoscale Metal-Organic Frameworks (NMOFs) silenced genes using Bcl-2, P-gp, and survivin siRNAs and the adsorption of pooled siRNA was made possible in this study by the Zn2+ metal linkage and cationic lipid coating of cisplatin, a prodrug-based bisphosphonate bridging ligand (He *et al.*, 2016). Pooled siRNA and cisplatin were more readily absorbed by cells as a result of this enhanced drug release (He *et al.*, 2015). Emerging strategies aimed at overcoming drug resistance in OSCC are summarized in Table 3.

RE-SENSITIZATION STRATEGIES

Utilizing Agents to Re-sensitize Cancer Cells to Chemotherapy

Agents that induce cancer cell re-sensitization to chemotherapy are critical in overcoming drug resistance, restoring the efficacy of conventional treatments. By triggering processes like medication efflux pumps, changed signalling pathways, or epigenetic changes, cancer cells frequently develop resistance. Re-sensitizing agents target these mechanisms to reverse resistance. For example, epigenetic modifiers like (HDAC) inhibitors and DNA methyltransferase inhibitors reactivate tumor suppressor genes, while efflux pump inhibitors block proteins like P-glycoprotein, preventing drug expulsion from cancer cells. Signal transduction inhibitors and apoptosis inducers target pro-survival pathways and restore cancer cells' ability to undergo programmed cell death. Additionally, hormonal modulators in hormone-dependent cancers can enhance chemotherapy response. These agents, used alongside chemotherapy, help improve therapeutic outcomes in resistant cancers (Ke *et al.*, 2017).

Metabolic Targeting to Disrupt Cancer Cell Survival under Drug Stress

Metabolic targeting is a strategy used to disrupt cancer cell survival, especially under drug pressure, by exploiting the altered metabolic pathways that cancer cells rely on for growth and survival. Cancer cells often shift their metabolism to adapt to harsh conditions, including chemotherapy-induced stress, by increasing glycolysis (Warburg effect), enhancing glutamine dependence, or activating fatty acid synthesis to meet their high energy and biosynthetic demands. Targeting these metabolic adaptations can make cancer cells more vulnerable to chemotherapy. For example, inhibiting glycolysis with agents like 2-deoxyglucose can reduce energy production in cancer cells, impairing their ability to survive drug treatment. Similarly, drugs that block glutamine metabolism, such as glutaminase inhibitors, deprive cancer cells of essential nutrients needed for growth. Additionally, targeting lipid metabolism through Fatty Acid Synthase (FASN) inhibitors can block membrane synthesis, further weakening cancer cell survival under drug pressure. By disrupting these metabolic pathways, cancer cells are less able to adapt and thrive, making them more susceptible to chemotherapy

Table 3: Emerging Strategies to Overcome Drug Resistance.

Strategy	Approach	Advantages	Limitations
Combination therapy	Chemotherapy + targeted agents	Enhanced efficacy	Increased toxicity
Nanotechnology	NMOFs, nanoparticles	Improved drug delivery	Translational challenges
RNA-based therapy	siRNA, miRNA	Gene-specific targeting	Stability issues
Immunotherapy	CAR-T, checkpoint inhibitors	Durable responses	Immune-related adverse events
Metabolic targeting	AMPK, FASN inhibition	CSC suppression	Early-stage research

and less likely to develop drug resistance. Metabolic targeting, when combined with conventional therapies, holds potential to improve treatment outcomes by cutting off the energy supply and biosynthetic resources that cancer cells depend on under drug pressure (Park *et al.*, 2020).

DISCUSSION

Overcoming chemoresistance in Oral Squamous Cell Carcinoma (OSCC) requires targeting key molecular pathways such as EGFR, PI3K/AKT/mTOR, NF-κB, and apoptosis regulators including Bcl-2. Emerging therapeutic approaches including targeted inhibitors, immunotherapies, and epigenetic modulators aim to disrupt these pathways and restore treatment sensitivity. Nanoparticle-based formulations and HDAC inhibitors offer additional opportunities by improving drug delivery, enhancing intracellular drug accumulation, and reactivating silenced tumor-suppressor genes. Precision-medicine strategies using biomarkers such as EGFR mutations, PD-L1 expression, and tumor mutational signatures enable the development of more individualized therapeutic regimens while minimizing toxicity. Advances in Next-Generation Sequencing (NGS) have significantly improved the understanding of genetic and epigenetic drivers of OSCC drug resistance, informing the development of targeted and combination therapies (Aliyari *et al.*, 2024).

However, despite considerable progress, challenges persist due to tumor heterogeneity, complex resistance mechanisms, and limitations in current preclinical models. Many studies rely heavily on *in vitro* drug-resistant OSCC cell lines, whereas only a limited number validate findings in animal models or clinical samples. Comparisons between drug-sensitive and drug-resistant models show consistent upregulation of PI3K/AKT, NF-κB, Wnt/β-catenin signaling, ABC transporters, and EMT markers in resistant cells. Yet, these findings are frequently correlative, and only a subset of studies incorporate rigorous controls such as untreated wild-type or isogenic cell lines. Evidence from clinical investigations remains scarce, highlighting a significant translational gap. The most reproducible and well-supported mechanisms across independent studies involve ABC transporter overexpression and PI3K/AKT-driven survival signaling. In contrast, mechanisms related to autophagy modulation and Cancer Stem Cell (CSC) plasticity show potential but require further verification in well-controlled preclinical and clinical settings. Incorporating comparative analyses across resistant versus sensitive models, as well as aligning preclinical findings with clinical outcomes, will be essential for identifying truly targetable vulnerabilities in OSCC. The Tumor Microenvironment (TME), including hypoxia, immune suppression, and stromal remodeling, contributes significantly to resistance by creating protective niches. Long non-coding RNAs (lncRNAs) have also emerged as important regulators of OSCC chemoresistance, influencing apoptosis, EMT, and drug efflux pathways. These insights underscore the need for combination strategies that target both intrinsic molecular pathways and extrinsic microenvironmental factors (Huang *et al.*, 2014).

Advances in pharmaceutical technologies such as CRISPR-Cas9 loaded nanoparticles, RNA-based therapeutics, ligand-targeted nanocarriers, and co-delivery systems combining small-molecule inhibitors with immunotherapy represent promising approaches to overcome resistance. Formulation-based strategies that improve bioavailability, bypass efflux pumps, enhance mucosal retention, and enable controlled drug release are particularly relevant for OSCC therapy (Meng *et al.*, 2021). Globally, the burden of OSCC continues to rise, especially in low- and middle-income countries where tobacco and alcohol use remain prevalent. Disparities in diagnosis and treatment access particularly delayed diagnosis in rural populations further worsen outcomes (Feng *et al.*, 2025). Therefore, improving early detection, integrating molecular diagnostics, and expanding access to precision-based therapies are critical components in addressing both the biological and socioeconomic challenges of OSCC (Ramalingam *et al.*, 2024).

CURRENT RESEARCH AND FUTURE PERSPECTIVES

A deformity that can be fatal, oral cancer is nevertheless very common throughout the world. Oral cancer accounts for over half of all oncology patients in several underdeveloped nations. Intervention in at-risk individuals is necessary to control the severe, broad effects of oral cancer, ideally before the illness becomes invasive but before it becomes locally progressed or metastatic. One popular and successful cancer treatment method is chemotherapy (Azwar *et al.*, 2021). However, an inducible cellular mechanism known as MDR may limit the cytostatic and cytotoxic effects of chemotherapy to induce apoptosis in

OSCC (Saha *et al.*, 2022). The function of TPL in controlling the efflux transporters to reverse MDR was demonstrated by a number of studies (Taniue *et al.*, 2021). *In vivo*, 5-fluorouracil and TPL (Triptolide) have synergistic anti-tumor activity against cancer-resistant xenografts (Taniue *et al.*, 2021). Moreover, TPL improves the anti-tumor effect of radiation therapy for the management of oral cancer (Kim *et al.*, 2023). In the future, several exciting research directions may offer fresh approaches to combating drug resistance. One innovative strategy to increase the efficacy of chemotherapy is the development of tailored medicines that precisely alter lncRNA activity. In order to accomplish this, mapping out the extensive networks of lncRNA interactions within cancer cells will require the integration of multi-omic methods including transcriptomics, proteomics, and genomes (Hussain *et al.*, 2025). A thorough understanding of the molecular pathways and ATFs involved in OSCC/HNSCC EMT has been made possible by numerous research. These revelations have raised the advantages of anti-EMT treatment. According to recent research, cancer cells may become sensitive to chemotherapeutic medicines using RNA interference (RNAi) techniques like miRNA. As a result, RNAi strategies, particularly siRNA, have been shown to repress and limit chemotherapy drug resistance genes in tumoral cells that have resisted chemotherapy. When using miRNA-based therapy, there are typically two approaches: miRNA masking and miRNA substitution. By inhibiting their target genes that are implicated in the development of cancer, including cancer medication resistance, oncomiRs and tumour suppressor miRNA replacement can control malignant cells (Shi *et al.*, 2019). Additionally, combining chemotherapeutic drugs with RNA interference (RNAi) strategies (siRNA or miRNA) may be a promising treatment for tumour cells that have resisted treatment. It has been demonstrated that metformin, vanadium, and other medications decrease mesenchymal differentiation markers including vimentin and N-cadherin while increasing the expression of E-cadherin. Combining chemotherapeutic drugs boosted drug sensitivity and decreased E-cadherin expression, which suppressed EMT, according to earlier *in vivo* investigations (Aliyari *et al.*, 2024). The intricate and varied molecular profiles of oral cancer have been better understood because of recent developments in the fields of molecular pathology and genetics. Recent discoveries of novel therapeutic drugs that target specific molecules or genetic defects implicated in the progression of cancer and resistance to treatment have been based on these results. The precise biomarkers that can be linked to clinical staging, therapy effectiveness, and post-treatment monitoring of patient recovery, however, are still up for debate (Coletta *et al.*, 2020). There are much less clinical longitudinal studies on the effectiveness of single or combination therapy in people with mouth cancer, and many important compounds that are being investigated in other malignancies are not being tried in oral cancer. Future studies should concentrate on examining the intricate genetic, epigenetic, and microenvironmental relationships that contribute to treatment failure in oral cancer, particularly about CSCs, which are increasingly recognised as the primary source of cancer recurrence and resistance to treatment. Cisplatin resistance in squamous cell carcinoma is caused by a variety of genes. Several genes, including several allegedly common drug-resistance-related genes, have been identified using microarray analysis of the model system for differentially expressed genes linked to cisplatin resistance in squamous cell carcinoma. This provides a logical foundation for identifying which pathways are suitable for more research and which molecular targets are viable targets for gene therapy (Hossain *et al.*, 2021). On the basis of these discoveries, additional research will provide light on the intricate molecular processes underlying medication resistance. Finding predictive indicators and treatment targets for HNSCC chemotherapy might be aided by research into the molecular mechanisms governing these alterations.

CONCLUSION

Chemoresistance in Oral Squamous Cell Carcinoma (OSCC) arises from multiple interconnected mechanisms, including genetic mutations, activation of survival pathways within the tumor microenvironment. These mechanisms collectively enable tumor persistence, recurrence, and reduced therapeutic responsiveness. Current therapeutic strategies such as small-molecule inhibitors, immune checkpoint blockade, nanocarrier-assisted drug delivery, and epigenetic modulators have shown promising preclinical results, yet direct clinical evidence in OSCC remains limited. Approaches like CAR-T cell therapy and CRISPR-based gene editing are still experimental, requiring further validation in well-designed *in vivo* and clinical studies specific to oral cancer. Importantly, mechanistic insights derived from other cancers (e.g., osteosarcoma or hypoxia models) provide useful conceptual parallels but should not be interpreted as direct evidence for OSCC. Future research should focus on integrating comparative studies across *in vitro, in vivo*, and clinical models, supported by biomarker-driven patient stratification to enhance therapeutic precision. Overall, a combination of targeted, immune, and nanotechnology-based strategies grounded in robust mechanistic and translational evidence holds potential to overcome drug resistance and improve patient outcomes in OSCC.

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ABBREVIATIONS

4E-BP1: 4E-binding Protein 1; **ABC:** ATP-Binding Cassette; **ADCC:** Antibody-Dependent Cellular Cytotoxicity; **Akt:** Protein Kinase B; **ALDH:** Aldehyde Dehydrogenase; **AMPK:** AMP-Activated Protein Kinase; **BAK:** BCL-2 Homologous

Antagonist Killer; **BAX:** BCL2-Associated X Protein; **BCL-A1A:** BCL-2-Related Protein A1A; **BCL-XL:** B-Cell Lymphoma Extra Large; **BCL-W:** B-Cell Lymphoma 2-Like 2; **BCRP:** Breast Cancer Resistance Protein; **CA IX:** Carbonic Anhydrase IX; **CAFs:** Cancer-Associated Fibroblasts; **CAR-T:** Chimeric Antigen Receptor T-Cell; **CSCs:** Cancer Stem Cells; **CTLA-4:** Cytotoxic T-Lymphocyte-Associated Protein 4; **DDR:** DNA Damage Response; **ECM:** Extracellular Matrix; **EGFR:** Epidermal Growth Factor Receptor; **eIF4E:** Eukaryotic Translation Initiation Factor 4E; **EMT:** Epithelial-to-Mesenchymal Transition; **FA:** Fanconi's Anaemia; **FASN:** Fatty Acid Synthase; **GLUT-1:** Glucose Transporter 1; **HDAC:** Histone Deacetylase Inhibitors; **HIFs:** Hypoxia-Inducible Factors; **HNSCC:** Head and Neck Squamous Cell Carcinoma; **IL-10:** Interleukin-10; **MAPK:** Mitogen-Activated Protein Kinase; **MCL1:** Myeloid Cell Leukaemia Sequence-1; **MDR1:** Multidrug Resistance Protein 1; **MDSCs:** Myeloid-Derived Suppressor Cells; **MET:** Mesenchymal-Epithelial Transition; **miRNA:** microRNA; **MMPs:** Matrix Metalloproteinases; **MRP:** Multidrug Resistance-Associated Protein; **MTD:** Maximum Tolerated Dosage; **NF-κB:** Nuclear Factor Kappa B; **NGS:** Next-Generation Sequencing; **NK cells:** Natural Killer Cells; **NMOFs:** Nanoscale Metal-Organic Frameworks; **OS:** Overall Survival; **OSCC:** Oral Squamous Cell Carcinoma; **OTS:** Osteosarcoma; **PD-1:** Programmed Cell Death Protein 1; **PD-L1:** Programmed Death-Ligand 1; **PFS:** Progression-Free Survival; **PI3K:** Phosphoinositide 3-Kinase; **RM SCCHN:** Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck; **RNAi:** RNA Interference; **RTK:** Receptor Tyrosine Kinase; **siRNA:** Small Interfering RNA; **SP:** Side Population; **TAAs:** Tumor-Associated Antigens; **TAMs:** Tumor-Associated Macrophages; **TGF-β:** Transforming Growth Factor Beta; **TKIs:** Tyrosine Kinase Inhibitors; **TME:** Tumor Microenvironment; **Tregs:** T-Regulatory Cells; **VEGF:** Vascular Endothelial Growth Factor; **VEGFR:** Vascular Endothelial Growth Factor Receptor.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTIONS

Kaniga Pandi - Writing-original draft. Binoy Varghese Cheriyan - methodology and supervision. Nimithasree Keerthivasan, Mridula Dhanapal Saravanan, Dhanavarsha Govindaraj - Investigation. Jai Anand Jagadeesan, Dinesh Kumar Eshwaravelu - Data curation. Vinayagam Srinivasan, Pandiyan Rajaguru - Conceptualization. Sowmiya Philip, Pradhosh Sakthivel, Rajeshkumar Thirupathi, Revathy Kumar - Formal Analysis.

SUMMARY

This review identifies the multifaceted drivers of drug resistance in OSCC, specifically highlighting the roles of the PI3K/Akt, NF-κB, and Wnt/β-catenin pathways, alongside EMT and Cancer Stem Cells (CSCs). The tumor microenvironment, particularly factors like hypoxia and cancer-associated fibroblasts, facilitates resistance through metabolic and signaling adaptations. The sources suggest that overcoming these challenges requires a multi-targeted approach integrating nanotechnology, RNA therapeutics, and immunotherapies such as CAR-T cell therapy and checkpoint inhibitors to improve treatment efficacy and patient survival.

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