An Update on Molecular Mechanisms and Targeted Therapiesto Combat Chemoresistance in Oral Cancer.

Sruthy Davis¹, Haris P.S.²

¹(Junior Resident, Oral Medicine and Radiology, Calicut government dental college, India)
²(Assistant Professor, Oral Medicine and Radiology, Calicut government dental college, India)

Corresponding Author: Sruthy Davis

Abstract: Patient survival rates of oral cancer have not changed significantly over the past year. Chemotherapy, surgery and radiotherapy are various treatment modalities for oral cancer. Drug resistance is the major barrier in the field of cancer treatment. Understanding molecular mechanism behind the chemo resistance is very critical to find ways to overcome this and to decrease mortality rates of oral cancer in future. This review explores current molecular mechanisms behind chemo resistance of oral cancer and targeted therapies to overcome chemo resistance.

Keywords: oral cancer, chemo resistance, molecular mechanisms, targeted therapies.

I. Introduction

Chemotherapy using cisplatin main treatment modality for oral cancer. It cannot achieve successful rate of survival rate among oral cancer patients due to chemo resistance. Chemoresistance may be acquired or intrinsic. It is peak time to find ways to overcome chemo resistance. Clearly, if drug resistance could be overcome, the impact on survival would be highly significant. So it is very important to know the molecular mechanisms of chemo resistance to target this resistance. In this article, the current understandings of molecular mechanisms of chemo resistance and targeted therapies to overcome were reviewed, including role of stem cells, epithelial mesenchymal transition, autophagy and miRNA.

A) The Key Players Of Chemoresistence-Stem Cells

Oral squamous cell carcinoma (OSCC), like many solid tumors, contains a heterogeneous population of cancer cells. Many recent studies proved the evidence of cancer stem cells are in this heterogeneous population of cells. Cancer stem cells have critical role in initiating, maintaining, and expanding the growth of tumor. Unfortunately this subpopulation (csc) also increase inertness of solid tumor including oral cancer for chemotherapy.

Altered gene expression and signaling pathway found among CSC compared to less bulk tumours. The basis of such resistance highlights the roles of ABC transporters, aldehyde dehydrogenase (ALDH) activity, intracellular signaling pathways, the DNA damage response, hypoxia and proliferative quiescence. There are a number of well-studied surface proteins and enzymatic processes that can be used to isolate cancer stem cells from the bulk of the other cancer cells. Three ATP-binding cassette (ABC)-superfamily multidrug efflux pumps are known to be responsible for chemo resistance; P-glycoprotein (ABCB1), MRP1 (ABCC1) and ABCG2 (BCRP). In a study conducted by Lo-Lin Tsai et al found Stem cells in oral cancer highly expressed stem-cell surface markers (CD117 and CD133) and the ABC trans-porter gene (ABCG2). Further, the chemo resistance of stem cells to cisplatin was possibly correlated with up regulation excision repair cross-complementation group 1 protein (ERCC1).

Therapeutic Implications: A study by M R Loebinger et al demonstrated drug-resistant stem cells, termed side population (SP) cells expressed both ABCG2 and ABC1 multidrug transporters and exhibited elevated Hoechst dye 33342 efflux indicated resistance to cytotoxic chemotherapeutic drugs including mitoxantrone. This finding may suggest novel approaches to oral cancer treatment, which could include the specific targeting of cancer stem cell. This study also shown that SP stem cell-like cells are rendered chemo sensitive using simple ABC transport inhibitors including verapamil and reserpine. A study by D Chen et al found by Targeting BMI1+ Cancer Stem Cells Overcomes Chemo resistance and Inhibits Metastases in Squamous Cell Carcinoma.
B) An Unforseen Role Of Epithelial–Mesenchymal Transition (EMT) In Chemoresistance

Studies provide evidence of the role of the epithelial–mesenchymal transition (EMT) as a critical mediator of cancer metastasis, but role in cancer drug resistance remains hidden. The epithelial–mesenchymal transition (EMT) is a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells; these are multipotentstromal cells that can differentiate into a variety of cell types. The changes in gene expression during EMT lead to numerous phenotypic changes, such as cell morphological changes, loss of adhesion and gain of stem cell-like features. Several key signaling pathways, including transforming growth factor beta (TGFβ), Wnt,Notch and Hedgehog, are known to be involved in EMT. Epithelial markers such as e-cadherin, cytokeratin, claudine, desmoplakin, beta keratin were down regulated in oral squamous cell carcinoma (OSCC), and mesenchymal markers such as N-cadherin, vimentin, fibronectin, and snail-1/2 were upregulated. The αVβ6 integrin, in particular, was postulated to modulate EMT in OSCC. Activation of the PI3K/Akt signaling pathway is a frequent event in human cancers, including OSCC. Recent study reported that Let-7d functions as novel regulator of epithelial-mesenchymal transition and chemo resistant property in oral cancer. The study showed that knockdown of let-7d promote epithelial-mesenchymal transition (EMT) traits and migratory/invasive capabilities in OSCC cells. Furthermore, down-expression of let-7d significantly activated Twist and Snail expressions and chemo-resistant abilities of OSCC cells.

Therapeutic Implications: Blocking induction of EMT and transcription factors (e.g. snail, slug, ZEB, and TWIST) can help decrease the chemotherapeutic resistance of cancer cells, shortening duration and preventing relapse. S100A4, a member of calcium-binding proteins, is directly controlled by Wnt/β-catenin signaling pathway as a master mediator in EMT. S100A4 knockdown in head and neck cancer stem cells reduced their self-renewal capability and their stemness and tumorigenic properties, both in vitro and in vivo. Conversely, S100A4 overexpression in HNSCC cells enhanced their stem cell properties. Immunohistochemical analysis of HNSCC clinical specimens showed that S100A4 expression was positively correlated with clinical grading, stemness markers, and poorer patient survival. Now research on therapeutic targeting S100A4 In a recent study by Cheng LH et al found by nullifying calcium binding ability S100A4 decrease in stemness property of cancer initiating cells of head and neck is achievable.

C) Role Of MicroRNA: Emerging Paradigm In Chemoresistence

MicroRNAs are encoded by genes located either in non-coding regions or in introns of protein coding genes and require a complex set of proteins for their formation. Several studies on head and neck cancer demonstrated aberrant expression of miRNAs is involved in proliferation, metastasis, chemoresistence, and radio resistance. Gusev Y et al in 2005 employed real time quantitative PCR - based methods to successfully identify microRNA deregulations in thirty two cancer cell lines including five from the head and neck/oral cavity. Hebert et al. in 2007 studied microRNA expression patterns in squamous cell cancer cells from the head and neck that were cultured under hypoxia conditions. Hypoxia is important in progression and treatment as it has been implicated in development of chemo resistance in head and neck/oral cancers. The results reflected profiling differences in the cancer cell lines and no nonmalignant controls were used, but the study associates hypoxia conditions with microRNA deregulation and potential development of resistance to chemotherapy. Identification of microRNA alterations in these conditions could facilitate our understanding of this adaptation by the cancer cell and guide targeted therapy. Yu et al. found a different expression of miRNAs between cisplatin-sensitive tongue squamous cell carcinoma and cisplatin-resistant sublines: in particular increased levels of let-7 family, miR-23a, miR-214, miR-518c, miR-608 and decreased levels of miR-21 and miR-342.

Therapeutic Implications: Cis-Dichlorodiammineplatinum (DDP) is the first-line choice for head and neck squamous cell carcinoma (HNSCC) including OSCC. But 70 to 80% of patients with relapsed or recurrent disease present resistant to DDP. In a study it found expression of Stat3 and Notch1 is associated with cisplatin resistance in head and neck squamous cell carcinoma. STAT3/miR-21 axis is the most extensively studied STAT3/miRNA interaction. It is well established that miR-21 is induced by IL-6/STAT3 activation in HNSCC. In a study by Xuan Zhou evaluated the effect of WP10666((STAT3 inhibitor) on the expression of STAT3 and miR-21.Treatment of DDP combined with WP1066 efficiently inhibited cell proliferation, migration and reverse chemo resistance.

D) The Critical Role Of Autophagy In Chemoresistance

Autophagy is a homeostatic cellular recycling and quantity control mechanism responsible for degrading unnecessary or dysfunctional cellular organelles and proteins in all living cells. Autophagy has dual roles in cancer, acting as both a tumor suppressor by preventing the accumulation of damaged proteins and organelles and as a mechanism of cell survival that can promote the growth of established tumors. Tumor cells activate autophagy in response to cellular stress and/or increased metabolic demands related to rapid cell proliferation. Autophagy-related stress tolerance can enable cell survival by maintaining energy production that
can lead to tumor growth and therapeutic resistance. As shown in preclinical models, inhibition of autophagy restored chemo sensitivity and enhanced tumor cell death.

**Therapeutic Implications:** Preclinical studies have shown that autophagy inhibition restored chemo sensitivity and increased the tumor cell death in various cancers. These results consolidated autophagy as a therapeutic target. This led to multiple clinical trials in humans to evaluate the potential role of autophagy inhibition using hydroxychloroquine (HCQ) in combination with chemotherapy or targeted agents. Protective autophagy can induced in oral cancer, by various compounds. In a study Wenyuan et al showed that exogenous C2-Ceramide caused caspase-3-independent apoptosis and programmed necrosis in HNSCC cells, as well as protective autophagy.

Short-chained ceramides encapsulated by nanocarriers and delivered intravenously or intraperitoneally have proven successful in inducing cell death without systemic side effects in multiple syngeneic and xenograft cancer models. Obatoclax is a small-molecule antagonist of the BH3-binding groove of anti-apoptotic BCL-2 family. In a study by Victor Y et al found obatoclax induced autophagy in all cancer cell lines, and the addition of the autophagy inhibitor chloroquine enhanced obatoclax cytotoxicity.

II. Conclusions and Future Perspectives

To get good success of chemotherapy, a better or full understanding of the mechanisms underlying chemo resistance is indispensable during tumor chemotherapy. Such new knowledge will be translated into the development of innovative cancer therapies to overcome resistance. Still, the multifactorial and redundant nature of tumor chemo resistance poses a significant barrier against the development of effective and safe chemo sensitization strategies.

**References**


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